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REVIEW ARTICLE

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Direct-acting antiviral agents for liver transplant recipients with recurrent genotype 1 hepatitis C virus infection: Systematic review and meta-analysis

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Abstract

Background: Comprehensive evaluation of safety and efficacy of different combinations of direct-acting antivirals (DAAs) in liver transplant recipients with genotype 1 (GT1) hepatitis C virus (HCV) recurrence remains limited. Therefore, we performed this systematic review and meta-analysis in order to evaluate the clinical outcome of DAA treatment in liver transplant patients with HCV GT1 recurrence.

Methods: Studies were included if they contained information of 12 weeks sustained virologic response (SVR12) after DAA treatment completion as well as treatment related complications for liver transplant recipients with GT1 HCV recurrence.

Results: We identified 16 studies comprising 885 patients. The overall pooled estimate proportion of SVR12 was 93% (95% confidence interval (CI): 0.89, 0.96), with moderate heterogeneity observed (τ^2 = 0.01, P < 0.01, I^2=75%). High tolerability was observed in liver transplant recipients reflected by serious adverse events (sAEs) with pooled estimate proportion of 4% (95% CI: 0.01, 0.07; τ^2 = 0.02, P < 0.01, I^2 = 81%). For subgroup analysis, a total of five different DAA regimens were applied for treating these patients. Sofosbuvir/Ledipasvir (SOF/LDV) led the highest pooled estimate SVR12 proportion, followed by Paritaprevir/Ritonavir/Ombitasivir/Dasabuvir (PrOD), Daclatasvir (DCV)/Simeprevir (SMV) ± Ribavirin (RBV), and SOF/SMV ± RBV, Asunaprevir (ASV)/DCV. There was a tendency for favoring a higher pooled SVR12 proportion in patients with METAVIR Stage F0-F2 of 97% (95% CI: 0.93, 0.99) compared to 85% (95% CI: 0.79, 0.90) for stage F3-F4 (P < 0.01). There was no significant difference between LT recipients treated with or without RBV (P = 0.23).

Conclusions: Direct-acting antiviral treatment is highly effective and well-tolerated in liver transplant recipients with recurrent GT1 HCV infection.

KEYWORDS
direct-acting antiviral, genotype 1, hepatitis C virus, liver transplantation, recurrence

Abbreviations: AE, adverse events; ASV, Asunaprevir; CsA, Cyclosporine A; DAA, direct-acting antiviral; DCV, Daclatavir; EASL, European Association for the Study of Liver Disease; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, Ledipasvir; LT, liver transplant; PrOD, Paritaprevir/Ritonavir/Ombitasivir/Dasabuvir; RBV, Ribavirin; RCT, randomized controlled trials; sAEs, serious adverse events; SMV, Simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

1 | INTRODUCTION

Liver cirrhosis and hepatocellular carcinoma (HCC) secondary to hepatitis C virus (HCV) infection are the leading causes for liver transplantation (LT) worldwide.[1,2] However, recurrent HCV infection post LT is a unique and difficult medical dilemma which occurs in over 90% of patients, and severe recurrent infection is observed in nearly 30% of patients within 3-5 years.[3,4] Thus, the allograft and recipient survival is closely correlated with the successful eradication of HCV.

Until very recently, interferon-based therapy was the only treatment option and rate of sustained virologic response (SVR) in these transplant recipients was merely 20%-30%.[5,6] The combination of direct-acting antiviral (DAA) agents, in the form of a first-generation protease inhibitor, telaprevir or boceprevir doubled the SVR rate at the expense of a series of adverse events (AEs) and serious adverse events (sAEs).[7,8] These included rashes, cytopenias, allograft rejection, severe anemia, and a mortality rate of 9% in one series. At the end of year of 2013, the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approvals of simeprevir (SMV) and sofosbuvir (SOF) heralded a new era in DAA therapy of HCV-related liver diseases. Consequently, the launches of several other second generation of interferon-free DAAs have opened a new scenario which revolutionized the treatment of chronic HCV infection in the general infected population. With a very favorable safety profile and high rates of SVR of over 95%,[9] the newer and all-oral DAA-based regimens have provided an unprecedented opportunity to cure HCV. Although HCV disease burden remains substantial for the time being, however, it is estimated that, within next decade, most patients with HCV infection would likely to attend SVR. Furthermore, SVR may forestall the progression of liver diseases with subsequent reduction in liver-related complications including HCC, hepatic decompensation, and both liver related as well as all-cause mortality.

HCV genotype 1 (GT1) is the most prevalent recurrence affecting the majority of patients post LT.[10,11] However, the effectiveness and tolerability of various of combinations of DAAs on specific genotype of HCV recurrence in LT recipients remain largely unknown.[12] In this study, we performed a systematic review and meta-analysis in order to provide a comprehensive, reliable, and up-to-date assessment of DAA treatment for GT1 HCV recurrence post transplantation. Our results may provide additional guidance for clinical practice and future research.

2 | MATERIALS AND METHODS

2.1 | Literature search

We have conducted a systematic search of various electronic databases, including Ovid Medline, EMBASE, Web of Science, Cochrane Database, and Google Scholar for relevant studies published from inception until July, 2018. The search was designed and conducted by an experienced medical librarian with input from the study investigators, using controlled vocabulary supplemented with keywords ("sofosbuvir" OR "ribavirin" OR "ritonavir" OR "asunaprevir" OR "simeprevir" OR "daclatasvir" OR "ombitasvir" OR "ledipasvir" OR "velpatasvir" OR "grazoprevir" OR "elbasvir" OR "DAA" OR "direct-acting antivirals" AND "liver transplantation" AND "hepatitis C" OR "HCV" AND "Genotype 1" OR "GT1") (Supporting Information method S1). In addition, the bibliographies of relevant review articles and all included studies were manually reviewed to identify relevant studies. No restrictions were applied to language due to the limited number of manuscripts. Abstracts from conferences were excluded in our database search. Besides, the reference lists of included articles and relevant systematic reviews were manually searched.

2.2 | Inclusion and exclusion criteria

All records identified through database searches were downloaded and duplicate records were removed. The title and abstract of remaining records were screened for relevance to liver disease and human subjects. After this initial screening, the lists of selected studies were cross-checked to resolve discrepancies. Subsequently, full articles were retrieved for detailed assessment.

Reports were included if they were original studies which contained at least five patients, presented effectiveness of treatment of second generation of interferon-free DAA regimens for at least 12 weeks in adult LT recipients with GT1 HCV recurrence. In addition, these included studies should present proportion of SVR12 after the end of the treatment. We excluded studies that enrolled LT recipients featured coinfection with hepatitis A, B, D, E virus or human immunodeficiency virus (HIV). Besides, studies without reporting AEs and/or sAEs were also excluded.

2.3 | Study selection and data extraction

Two reviewers (JL and BM) worked independently to determine whether a study met inclusion criteria, abstracted information to assess the methodological validity of each candidate study, and extracted data with structured data collection forms. The reviewers resolved discrepancies by jointly reviewing the study in question. If no consensus was reached, a third reviewer (QP), unaware of prior determinations, functioned as an arbiter.

Extracted information for this study include study design, immunosuppression protocols, dosage adjust, DAA combinations, collaboration (single or multicenter) and patient demographics including age, gender, ethnicity, viral load, degree of fibrosis. We also obtained data of treatment outcomes of SVR12. In addition, data about the tolerability of DAA treatment were also collected.

2.4 | Quality assessment

The quality of included studies was rated using the institute of Health Economics (IHE) quality appraisal checklist, which is usually employed for assessment of the quality of case series. As all of the included studies were single-arm reports, an assessment tool for case series is more suitable than the Newcastle Ottawa Scale (NOS). In this 20-item checklist, both risk of bias

and quality of reporting were scored by yes, no, or partial/unclear answers. Eight quality parameters including study objective (0-1 points), study design (0-3 points), study population (0-3 points), intervention and co-intervention (0-2 points), outcome measure (0-4 points), statistical analysis (0-1 points), results and conclusions (0-5 points), and competing interests and sources of support (0-1 points) were used to assess included studies. In our analysis, studies with 0-2, 3-5, 6-8, and ≥9 points were considered as having low, moderate, high, and very high risk of bias, respectively. Quality assessment was done by two independent authors (JL and BM), and disagreements were solved by the third author (QP).

2.5 | Statistical analysis

After checking for consistency, the Metaprop module in the R-3.4.2 statistical software package was used for the meta-analysis. Given that, the SVR12 proportion in many articles are close to 100%. So the

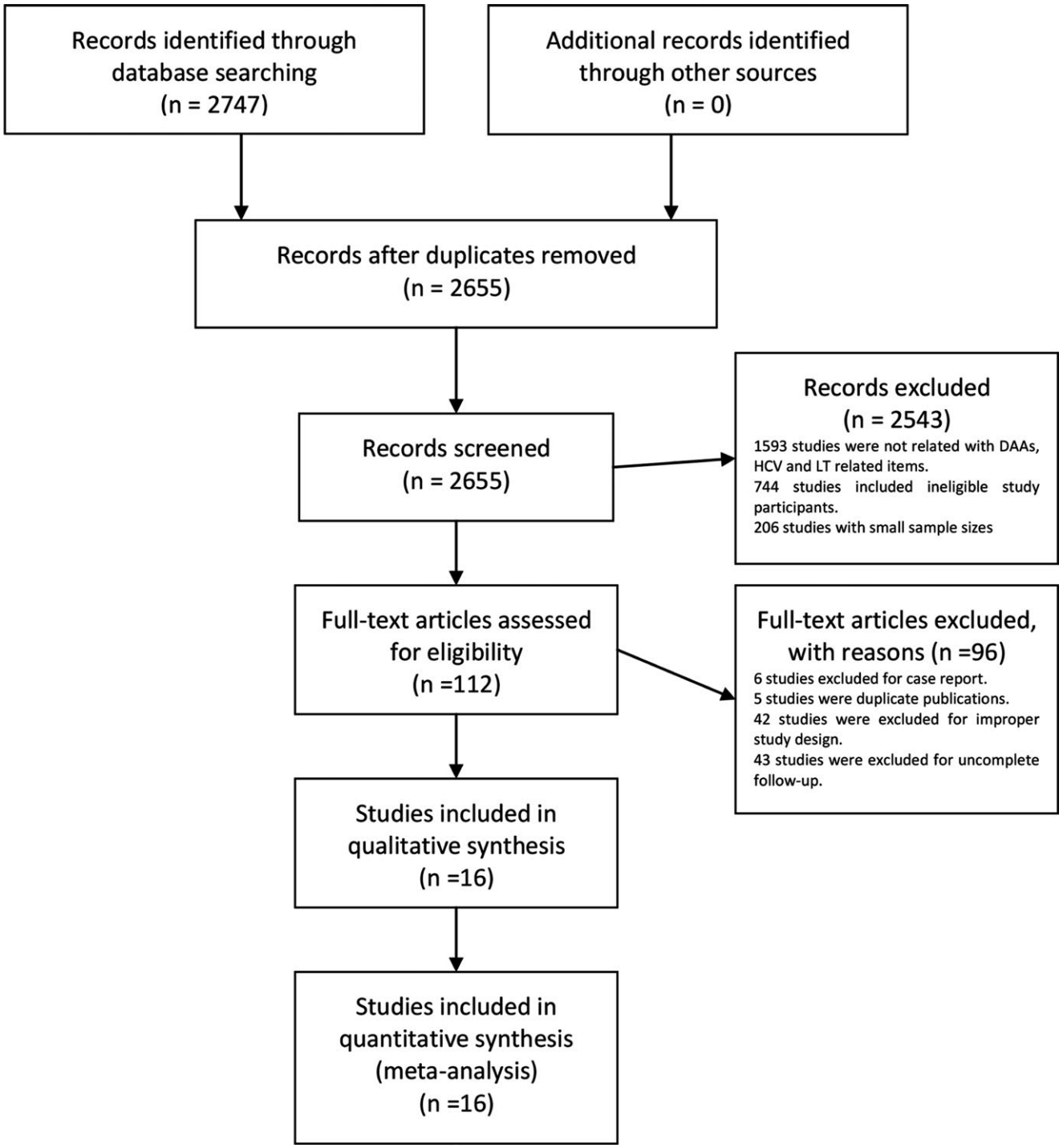

FIGURE 1 Flow chart for the systematic review and meta-analysis of the literature

proportion of SVR12 reported in each study was Free-Turkey double arcsine transformed prior to compute the pooled estimate rate. A 95% confidence interval (CI) was estimated using Wilson score method. We performed meta-analysis of proportion to compute the pooled estimate proportions using a random effects model (DerSimonian-Laird Method). Heterogeneity across the included studies was assessed using the Cochran Q-statistics and I^2 statistics, with I^2 statistics 25%-50%, 50%-75%, and >75% considered as mild, moderate, and severe heterogeneity, respectively. Based on the available data, subgroup meta-analysis were performed using the Q test to determine whether the pooled estimate proportion of SVR12 varied by study type (retrospective study or perspective study), with or without Ribavirin (RBV), METAVIR score (F0-F2 or F3-F4), and different kinds of regimens SOF/SMV with or without RBV, SOF/Ledipasvir (LDV), Asunaprevir (ASV)/SMV, Daclatasvir (DCV)/SMV with or without RBV and Paritaprevir/Ritonavir/Ombitasivir/Dasabuvir (PrOD). Funnel plots and Egger regression test were used to assess potential publication biases.

Ethical approval or inform consent from patients was not required, because our data were extracted from previous studies. Nevertheless, the included studies in our review did obtain patient consent and each study was approved by ethics committee.

3 | RESULTS

3.1 | Literature search

Our search strategy identified 2747 articles for inclusion. After removing duplicate studies, 2655 studies were further evaluated for eligibility. Of these, 1593 studies were excluded, which had no DAA, HCV GT1, or LT-related items. After screening the titles and abstracts, another 950 studies were excluded; 744 studies of them included ineligible study participants, 206 with small sample size. Finally, 112 studies were retrieved and evaluated in full text. Of those reviewed in detail, 96 studies were excluded due to duplicate publication, improper study design, or incomplete information of effectiveness and tolerability. Eventually, 16 studies, published until July 2018, involving 885 patients were eligible for the qualitative and quantitative synthesis as detailed in Figure 1. Based on the Institute of Health Economics (IHE) quality appraisal checklist, six studies were of low risk of bias compared to 10 studies with moderate risk of bias. To date, no randomized controlled trial has been published exploring the efficacy and tolerability of DAAs on recurrence of post LT. The 16 included studies were performed by five different countries. Among them, 62.5% were conducted in USA, 18.75% in Japan, 6.25% in UK, 6.25% in Germany, and 6.25% in Spain. Ten of the included studies were multicenter studies and six were single-center studies. All of these studies were published in full text.

3.2 | Baseline characteristics

Tables 1 and 2 summarize the baseline patient demographic and clinical characteristics. Except one study[13] that did not report patient ethnicity, the majority of patients were Caucasian, male, with a mean age of approximately 60-year-old, had GT1a HCV recurrence, and received tacrolimus as part of their immunosuppressive treatment. Five different DAA combination protocols were described: SOF/SMV with or without RBV (n = 8)[13-20]; SOF/LDV (n = 3)[21-23]; ASV/SMV (n = 2)[24,25]; DCV/SMV with or without RBV (n = 2)[26,27]; PrOD (n = 1).[28] Detailed baseline characteristics of the included studies are provided in Tables 1 and 2.

TABLE 1 Baseline characteristics of studies included

Author	Year	Cases	Study design	Ethnicity (C/B/A/H/O)	Genotype 1a (%)	Male (%)	Age(Years)	Collaboration
Jacqueline	2016	46	Prospective	37/8/1/0/0	33 (71.7%)	34 (73.9%)	60 (49-68)	Multiple-center-
Robert	2016	151	Prospective	118/14/0/0/19	87 (57.6%)	112 (74.2%)	61 (46-78)	Multiple-center
Lutchman	2016	50	Retrospective	25/0/0/16/9	32 (64.0%)	42 (84.0%0	61.3 ± 7.1	Single-center
Suraki	2015	123	Retrospective	91/12/0/12/8	74 (60.2%)	93 (75.6%)	61 ± 6	Multiple-center
Saro	2015	32	Retrospective	11/0/2/19/0	22 (68.8%)	21 (65.6%)	58 (47-71)	Single-center
Jackson	2016	67	Retrospective	-	23 (34.3%)	46 (68.7%)	61.5 ± 6.6	Multiple-center
Punzalan	2015	42	Retrospective	34/1/1/6/0	33 (78.6%)	28 (66.7%)	58	Single-center
Toru	2017	74	Retrospective	0/0/74/0/0	-	32 (43.2%)	62.7 ± 4.5	Multiple-center
Kerstin	2015	6	Retrospective	6/0/0/0/0	5 (83.3%)	5 (83.3%)	58.5 (50-63)	Single-center
Masaki	2017	9	Retrospective	0/0/9/0/0	-	5 (55.6%)	64.7 ± 0.85	Single-center
Neil	2015	56	Retrospective	48/0/0/0/8	44 (78.6%)	42 (75.0%)	61	Multiple-center
Paul	2014	34	Prospective	29/4/0/0/1	29 (85.3%)	27 (79.4%)	59.6 ± 6.6	Multiple-center
Yoshihide	2017	54	Retrospective	0/0/54/0/0	-	25 (46.3%)	64 (47-77)	Multiple-center
Mohamed	2017	60	Retrospective	53/0/0/0/7	47 (78.3%)	42 (70.0%)	59.9 ± 7.25	Single-center
Mohamed A	2016	46	Retrospective	32/0/0/0/14	26 (56.5%)	32 (69.6%)	62.0 ± 8	Multiple-center
Xavier	2016	35	Prospective	34/0/0/0/1	-	22 (62.9%)	62 (27-69)	Multiple-center

A, Asian; B, black; C, Causian; H, Hispanic; O, others.

3.3 | Outcomes

3.3.1 | The efficacy and tolerability of DAA treatment

Once DAA treatment completed, patients were followed up for evaluating SVR12 proportion. In total, 805 out of 885 (91.0%) patients successfully achieved SVR12. The pooled estimate SVR12 proportion among all LT recipients were 93% (95% CI: 0.89, 0.96), with moderate heterogeneity observed in a random effects model (τ^2=0.01, P < 0.001, I^2=75%, Figure 2). The expected shape observed in the funnel plots and results of the Egger's test (P = 0.44) indicated no significant publication bias (Figure S1 and S2). AEs commonly occurred in these patients. General symptoms including fever, fatigue, and dizziness were the most common AEs with pooled estimate rate of 37% (95% CI: 0.14, 0.64; τ^2 = 0.30, P < 0.01, I^2 = 98%, Random effects model, Figure S3). Pooled estimate incidence rate of gastrointestinal AEs was 10% (95% CI: 0.02, 0.23; τ^2 = 0.11, P < 0.01, I^2 = 96%, Random effects model, Figure S4) and pooled estimate incidence rate of skin problems was 7% (95% CI: 0.02, 0.15; τ^2 = 0.06,

TABLE 2 Baseline characteristics of studies Included

Author	Immunosuppressive protocols	Dosage adjust	Viral Load Log IU/mL	DAAs protocol	Duration of DAA treatment	Duration from LT (M)
Jacqueline	TAC 89%, MMF 41%, SIR 11%	15 pts underwent dosage adjust	5.8	SOF+SMV ±RBV	12/24 wk	54 (9-171)
Robert s.	TAC 80%, CsA 10%, both 0.6%; MMF/MPA 40%	NR	-	SOF+SMV±RBV	12 wk	60 (0-276)
Lutchman	96% TAC	1 pts changed cyclosporin into TAC	6.3 ± 1.2	SOF+SMV	12 wk	-
Suraki	TAC 91%,CsA 8%	NR	-	SOF+SMV+RBV	12 wk	57 ± 65
Saro	TAC 66%, CsA 3%, RAP 3%, TAC+MMF 25%, CsA+MMF 3%	NR	6.58	SOF+SMV	12 wk	48 (7-166)
Jackson	TAC 84%, CsA 6%, SIR 6%	NR	-	SOF+SMV	12 wk	-
Punzalan	TAC 88%,CsA 7%,RAP 5%	7 pts TAC dosage decreased	-	SOF+SMV	12 wk	-
Toru	TAC 45%, TAC+MMF 45%, TAC+MMF+STE 45%, MMF 4%, CsA 1%	NR	6.3	ASV+DCV	24 wk	-
Kerstin	-	No change	6.06	DCV+SMV	24 wk	15 (6-162)
Masaki	TAC 56%+MMF, MMF 22%, TAC 11%, CsA+PRED 11%	NR	6.11	ASV+DCV	24 wk	70 (3-121)
Neil	CsA 9%, TAC 71%, MPA 2%, SIR 18%	8pts TAC dosage increased, 9 pts decreased; 2pts CsA dosage decreased; 3 pts SIR dosage increased, 3pts decreased	-	SOF+SMV±RBV	12 wk	53
Paul	TAC 85%, CsA 15%, MMF 32%, PRED 6%	No change	6.6	PrOD	12 wk	-
Yoshihide	TAC 75%, MMF 46%, PRED 28%	NR	6.5	LDV+SOF	12 wk	61 (1-158)
Mohamed	-	NR	-	LDV+SOF	12 wk	42 (11-113)
Mohamed A	TAC 76%, SIR 13%, CsA 9%, EVR 2%, MMF 33%	Minimal changed but details not report	7.79	LDV+SOF	12/24 wk	30 (2-117)
Xavier 2016	TAC 71%, CsA 29%	NR	6.9	SMV+DCV+RBV	24 wk	47 (14-114)

ASV, Asunaprevir; CsA, Cyclosporine A; DAAs, direct-acting antivirals; DCV, Daclatavir; EVR, Everolimus; LDV, Ledipasvir; m, months; MMF, Mycophenolate Mofetil; MPA, Mycophenolic Acid; PrOD, Paritaprevir/Ritonavir/Ombitasivir/Dasabuvir; Pts, patients; PRED, Prednisone; RAP, Rapamune; RBV, Ribavirin; SIR, Sirolimus; STE, Steroid; SOF, Sofosbuvir; SMV, Simeprevir; TAC, Tacrolimus.

TABLE 3 Incidence of adverse events and serious adverse events during direct-acting antivirals treatment for patients of hepatitis C virus genotype 1 recurrence post liver transplantation

	Jacqueline 2016	Robert 2016	Lutchman 2016	Suraki 2015	Saro 2015	Jackson 2016	Punzalan 2015
GI Symptoms							
Nausea	23.9%	11.3%	4.4%	5.0%	3.0%	11.3%	
Diarrhea	21.7%						
Vomitting	17.4%						
Constipation	10.9%						
De-or increased appetite	13.0%		4.4%		3.0%		
General Symptoms							
Perspiration							
Cough							
Insomnia	13.0%		35.9%	2.0%			
Dizziness					9.0%		
Fever					3.0%		
Headache	37.0%	18.5%	8.7%	5.0%	25.0%	18.5%	
Fatigue	34.8%	25.2%	44.6%	13.0%	22.0%	25.2%	2.4%
Skin Problems							
Photosensitivity, pruritus, rash	21.7%	13.9%	44.6%	6.0%	6.0%	13.9%	12.0%
Anemia	10.6%			77.0%		10.6%	
Dysnoea	28.2%			4.0%			
Infection and infestation		14.6%				14.6%	
Joint or muscle pain			4.4%		9.0%		2.4%
Others		11.9%		14.0%			21.5%
sAEs	10.9%	11.9%	6.5%	2.4%	0	11.9%	2.4%

GI, gastrointestinal; sAEs, serious adverse events.

$P < 0.01$, $I^2 = 93\%$, Random effects model, Figure S5). SAEs were mainly associated with kidney injury, were reported in 45 patients, and 12 patients died during the treatment period (Table 3). The pooled estimate rate of sAEs was 4% (95% CI: 0.01, 0.07, $\tau^2 = 0.02$, $P < 0.01$, $I^2 = 81\%$, Random effects model, Figure 3).

3.3.2 | Study design

Twelve retrospective and four prospective studies were included. There was no significant difference in pooled estimate SVR12 proportion when comparing studies of prospective, 91% (95% CI: 0.87, 0.95), versus retrospective, 93% (95% CI: 0.88, 0.97) ($P = 0.44$, Figure S6, Random effects model).

3.3.3 | Degree of liver fibrosis

The METAVIR Fibrosis Score, simply put, is a evaluate system to determine the level of liver fibrosis.[29] The METAVIR Fibrosis Score grades the degree of fibrosis on a 5-point scale from 0 to 4. Fibrosis scores range from F0 to F4 (F0 stage, no fibrosis; F1 stage, portal fibrosis without septa; F2 stage, portal fibrosis with septa; F3 stage, numerous septa without cirrhosis; F4 stage, cirrhosis). A total of eight studies evaluated the levels of fibrosis and cirrhosis of patients according to METAVIR Fibrosis Score. The pooled SVR12 rate estimates among patients with METAVIR Fibrosis Score for F0-F2 stages were 97% (95% CI: 0.93, 0.99) compared to 85% (95% CI: 0.79, 0.90) for stages F3-F4. There was a trend for a higher SVR12 rate in patients with F0-F2 stages than patients with F3-F4 stages ($P < 0.01$, Figure 4, Random effects model).

3.3.4 | Different combination of DAA regimens

Sixteen studies which contained five different DAA regimens were administered into clinical treatment of LT recipients with recurrent GT1 HCV infection. The pooled estimate SVR12 proportion were 97% (95 CI: 0.89, 1.00), 81% (95% CI: 0.72, 0.89), 100% (95% CI: 0.98, 1.00), 90% (95% CI: 0.80, 0.97), and 90% (95% CI: 0.87, 0.92) among patients who underwent treatment of PrOD, ASV/DCV, LDV/SOF,

Toru 2017	Kerstin 2015	Masaki 2017	Neil 2015	Paul 2014	Yoshihide 2017	Mohamed 2017	Mohamed A.2016	Xavier 2016
			36.0%	24.0%		3.0%		
				26.0%	2.0%			14.0%
	30.0%		21.0%					
	17.0%							
				32.0%				14.0%
			21.0%	26.0%			5.0%	
			7.0%	18.0%				
			36.0%	44.0%		23.0%	5.0%	14.0%
	50.0%		71.0%	50.0%		20.0%	6.0%	9.0%
			35.0%	21.0%				31.0%
	30.0%			29.0%				54.0%
								11.0%
					2.0%			
			7.0%	39.0%				
20.2%		22.2%	28.0%	42.0%	10.0%			
0	0	0	3.6%	6.0%	13.0%	0	0	23.0%

SMV/DCV with or without RBV and SMV/SOF with or without RBV, respectively (Figure S7, Random effects model).

3.3.5 | With or without RBV

A total of 124 LT recipients used RBV as combinational treatment compared to 761 recipients without. The pooled estimate SVR12 proportion of recipients treated with RBV was 90% (95%CI: 0.84, 0.94). For recipients treated without RBV, the pooled proportion was 94% (95%CI: 0.89, 0.97). There was no significant difference in SVR12 proportion between LT recipients treated with or without RBV (P = 0.23, Figure S8, Random effects model).

4 | DISCUSSION

The current systematic review and meta-analysis included 16 studies comprising 885 patients to assess the outcome of DAA treatment for liver transplant recipients with recurrent GT1 HCV infection. Overall, the pooled SVR12 and sAEs proportion were 93% and 4%, representing a rather good outcome. Subgroup analyses revealed clear difference in SVR12 rates for different treatment strategies. The pooled estimate proportion for combination of LDV/SOF appears much higher than the other four combinations. In addition, the efficacy of DAA treatment is closely associated with fibrosis or cirrhosis levels, which highlights the necessity of early initiation of DAA treatment in these patients.

The pooled estimate results of SVR12 provided evidence that DAA treatment was clinically effective in eradicating GT1 HCV recurrence post LT. This is comparable to the pooled estimate results from a recent meta-analysis that contained all HCV GTs.[30] Of note, the unbalanced application of DAAs for GT1 HCV recurrence exists among different regions. There is a trend that the first-class of DAAs are commonly used in European or North American countries. For many countries, even like Japan, cost-effectiveness other than SVR rate is the first consideration for clinicians.[24,25] However, in Asia-pacific or Africa countries, HCV has distinct epidemiology. Furthermore, DAA availability has been delayed due to economic constraints and regulatory rules.[31] Although two studies from Japan

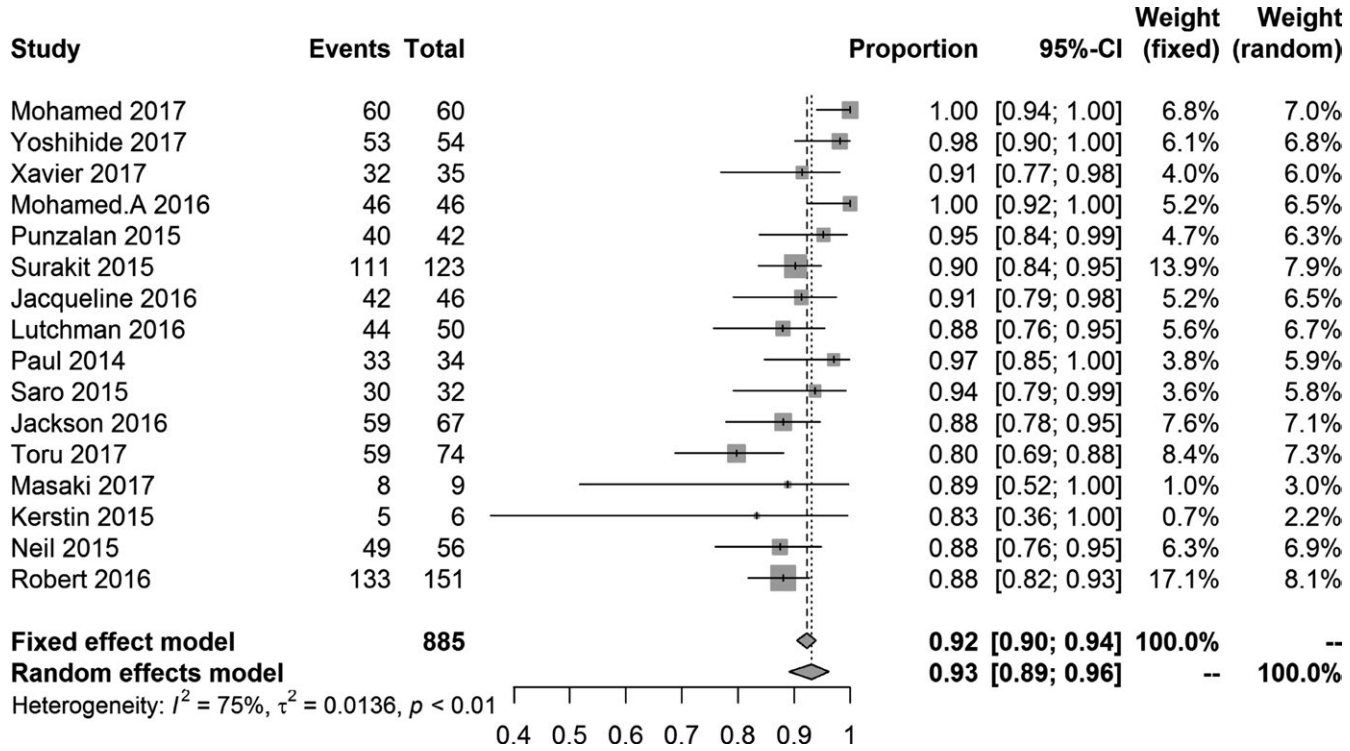

FIGURE 2 Pooled estimate proportion of 12 weeks sustained virologic response after treatment completion and 95% confidence interval after direct-acting antivirals treatment of GT1 HCV recurrence post liver transplantation from 16 studies. Abbreviations: CI, confidence interval; Events, the number of patients who reached SVR12; Total, the number of patients analyzed

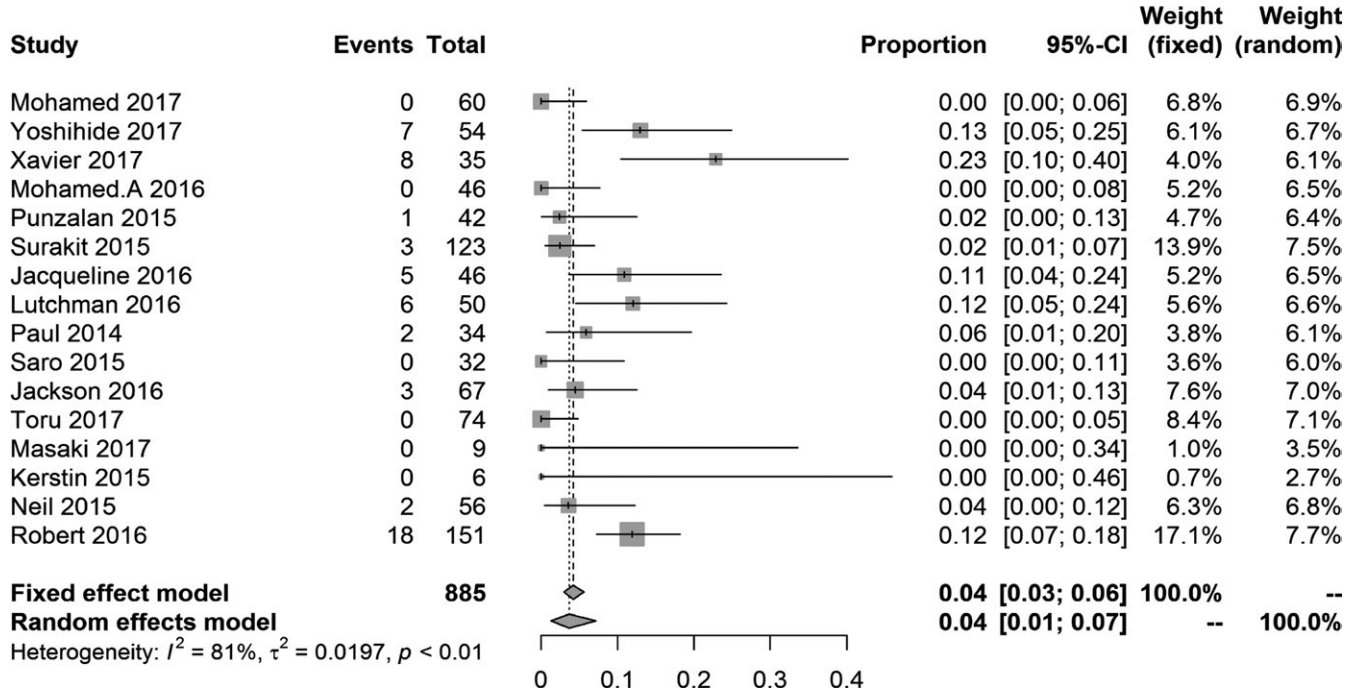

FIGURE 3 Pooled estimate proportion of serious adverse events and 95% confidence interval after direct-acting antivirals of GT1 HCV recurrence post liver transplantation from 16 studies. Abbreviations: CI, confidence interval; Events, the number of patients who reached SVR12; Total, the number of patients analyzed

suggested that DAA treatment is effective in Asian patients, multiregional and systematic studies should be combined to further confirm the effectiveness of DAA treatment for different regions.

The average time of progression from initial HCV infection to cirrhosis is about 30 years, but 20%-30% of liver transplant recipients develop cirrhosis within 5 years.[32] Retransplantation is the only

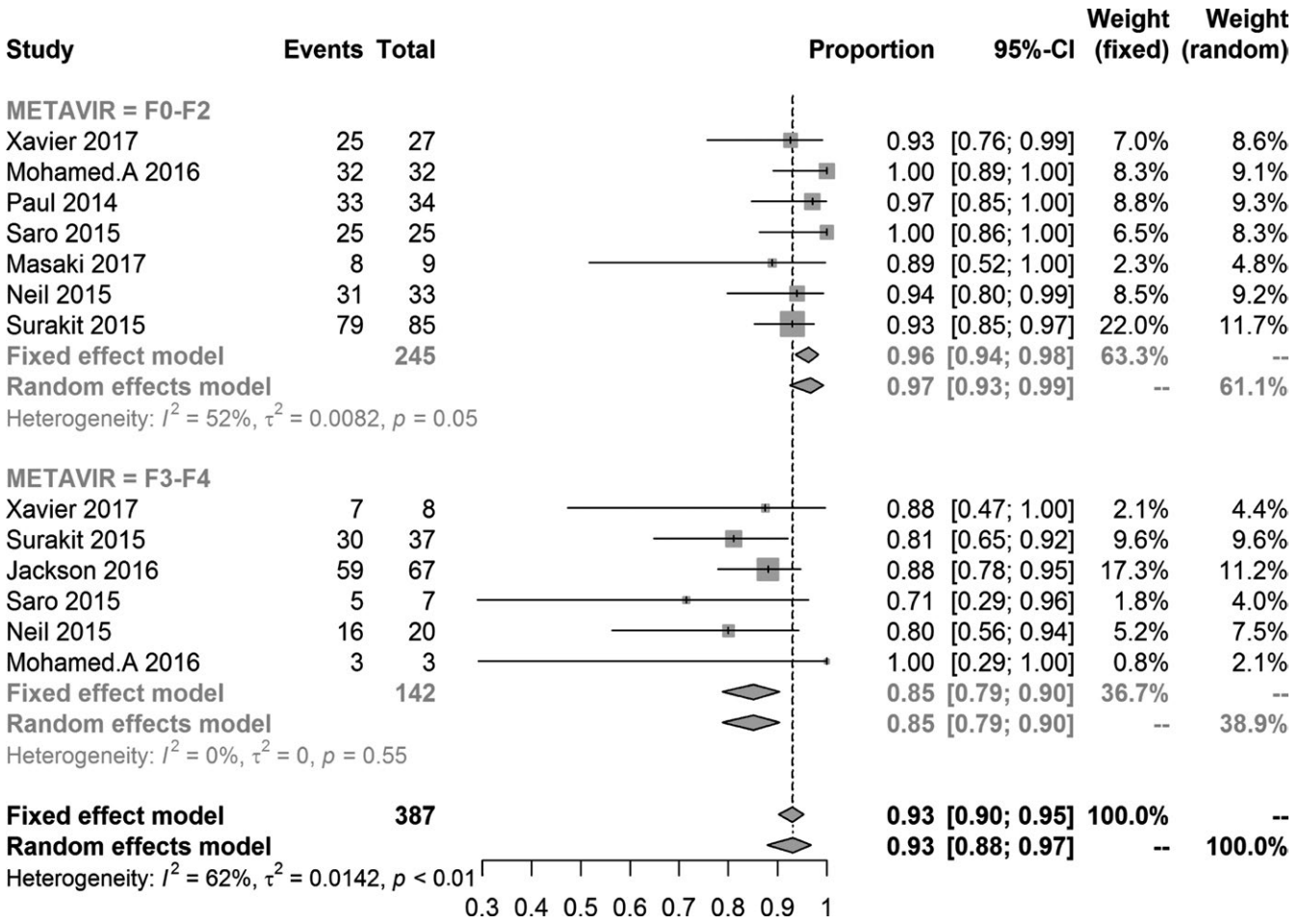

FIGURE 4 Comparison of pooled estimate proportion of 12 weeks sustained virologic response after treatment completion and 95% confidence interval between METAVIR Fibrosis Stages F0-F2 and F3-F4 after direct-acting antivirals treatment of hepatitis C virus genotype 1 recurrence post liver transplantation. Abbreviations: CI, confidence interval; Events, the number of patients who reached SVR12; Total, the number of patients analyzed

option to achieve long-term survival of patients with decompensated cirrhosis. However, due to organ shortage and poor clinical outcome, retransplantation is clearly not a sustainable solution.[33] In our subgroup analysis of liver transplant recipients with SVR12 rate and fibrosis data (METAVIR Fibrosis Score), our detailed analysis supports the latest evidence-based guidelines that DAAs also can be effectively used in eradicating HCV in patients with advanced fibrosis or cirrhosis post LT.[34] We observed a higher SVR12 pooled estimate proportion in patients with mild fibrosis compared with those of advanced fibrosis or cirrhosis, with a trend favoring SVR12 in patients with mild fibrosis. Our results indicated that the capability of HCV eradication by DAAs may be correlated with the levels of liver fibrosis or cirrhosis. Therefore, DAA treatment is recommended to be initiated early after transplantation.

Five different combinations of DAA treatment were identified in our systematic review and meta-analysis. There are important differences among the strategies, such as addition of RBV, duration of treatment, and potential drug interactions. Among these regimens, SMV/SOF with or without RBV were most commonly used with a pooled estimate SVR12 proportion of 90%, which is comparable with a recent study reporting SVR12 rate of 88%.[30] A number of studies have pointed out that SMV may interact with Cyclosporine A (CsA), and therefore the immunosuppressant tacrolimus is recommended to be used.[35] In general, the combination of SMV and SOF with or without RBV seems to be a safe regimen even at the early stage of post transplantation, when constant changes of immunosuppressive medication are often required and the patients are vulnerable to side effects. The combination of LDV and SOF has been used in three studies. The safety and efficacy of combination of LDV and SOF was firstly confirmed in a US-based SOLAR-2 study with a SVR12 rate of 96% and SVR24 rate of 98%.[36] The pooled estimate SVR12 proportion of LDV and SOF from our study is as high as 100%. Only one study reported their results for the DAA combination regimen of PrOD in GT1 HCV recurrence post LT with SVR12 proportion of 97%. Unfortunately, PrOD is contraindicated in patients with cirrhosis and has a potential to increase the plasma CsA levels by five to six folds and tacrolimus levels by 60-85 folds, which limited its clinical application.[28] In addition, efficacy and safety were not established for shorter duration therapy, or more advanced fibrosis/cirrhosis in a real world setting. Combination of ASV and DCV

were administered by two Japanese studies with the lowest pooled estimate SVR12 proportion of 81%. Although this combination had a cost-effective advantage, increased transaminase levels were commonly associated with ASV.[37,38] Two studies have reported a pooled estimate SVR12 proportion of 90% with DAA combination of SMV/DCV with or without RBV. Although the pooled estimate SVR12 proportion was satisfactory, two limitations including small sample size and prolonged treatment period of 24 weeks in these two studies should be noted.

There is ongoing debate whether adding RBV to interferon-free treatment strategy is necessary for treating HCV recurrence after LT.[16] RBV has been used for over 40 years in combination for treating HCV with an obscure understanding of its mechanism-of-action.[39,40] What is clear, however, is adverse effects. Hemolytic anemia has been observed in about one third of the patients. Lymphopenias, pruritus, and rash also commonly occur. Thus, patients treated with RBV often need a close monitoring and dose adjustment, especially for those with chronic kidney disease. It is also recommended that patients treated with RBV should undergo at least 6-month washout period due to the possible teratogenic and embryocidal effects.[40-42] In current study, we observed an increased pooled estimate incidence rate of sAEs in patients treated with RBV, in accordance with the results from previous studies. Given that a number of studies have pointed out RBV were not correlated with an increased SVR12 rate,[13,16,20,43] we compared patients treated or not treated with this medication. Our results also indicated that RBV was not correlated with an increased pooled estimate SVR12 proportion. We also assessed the tolerability of DAA treatment by analyzing pooled estimate proportion of AEs and sAEs. General symptoms, gastrointestinal symptoms, and skin complaints were presented with a pooled estimate incidence rate of 37%, 10% and 7%, respectively. SAEs including death caused by hepatic or renal failure, pneumonia, bone marrow failure, acute kidney, liver or other major organ infection, hepatic decompensation, spontaneous bacterial peritonitis, and sepsis, were analyzed with a pooled estimate incidence rate of 4% (I^2 = 81%).

Among them, renal dysfunction was reported in 45 patients, and 12 patients died during the treatment period. Impaired renal function commonly occurred in liver transplant recipients with the prevalence ranging from 17% to 95%.[44,45] Approximately 40% of these patients had already experienced a hepatorenal syndrome pretransplantation.[46] In addition, toxic reasons, ischemia reperfusion and Calcineurin Inhibitor (CNI)-associated nephropathy were account for renal dysfunction post transplantation.[47] Although the exact pathophysiological mechanisms are not fully understood, HCV infection may influence renal function through different pathways.[48] A recent study documented that those patients with HCV recurrence after LT will absolutely benefit from HCV elimination but will be at a higher risk for renal dysfunction or failure associated with antiviral drugs like SOF.[49] Unlike most DAAs, the nucleotide analogue NS5B polymerase inhibitor SOF was renally excreted. For area under the curves (AUCs) of SOF, patients with end-stage renal diseases was 45-fold and 35-fold higher compared to normal renal function when dosed 1 hour before or 1 hour after hemodialysis, respectively.[50] However, there are conflicting data about the application of SOF in clinical treatment. Saxena et al [51] evaluated the safety and efficacy of SOF-based therapy in HCV-infected patients with impaired renal function. High-SVR rate of 83% was achieved with high rate of renal dysfunction and sAEs observed. A prospective multicenter cohort study enrolled 50 patients with Glomerular Filtration Rate (GFR) <35 mL/min per 1.73 m^2 for treatment with a SOF-based therapy. All genotypes were included and more than half of them were cirrhotic patients. The results indicated that there is no significant change in GFR for patients who were not on dialysis.[52] More recently, Teegen et al [49] also documented that a dose reduction for SOF did not seem to be necessary to prevent further renal damage. Thus, additional data are still needed to further assess the safety of SOF in transplant recipients.

CNIs are the backbone of immunosuppressive treatment of LT. Eighty percent of liver transplant recipients were using tacrolimus alone or in combination with mycophenolate 1 year post transplantation.[53] Although CNIs can reduce the incidence of acute injection and improve overall survival, they are inevitably associated with nephrotoxicity which is reflected in tubular atrophy, interstitial fibrosis, and glomerulosclerosis on kidney biopsy.[54] However, so far, the use of a CNI-free regimen is still challenging and the trend in LT was to use regimens that minimize the use of CNIs in combination with mycophenolate mofetil (MMF) or mammalian target of rapamycin inhibitors. One important observation, the use of everolimus with reduced tacrolimus exposure helped to preserve renal function after 3-year follow up which indicated that consideration should be given to minimize the dose of CNIs or switch to MMF or everolimus for these patients.[55,56]

This study has exclusively focused on the effectiveness and tolerability of DAA treatment. Thus, a control group is not included, such as patients treated with DAAs before LT or treated with interferon post LT. Thus, without such a control, we cannot conclude whether treatment post LT has any advantage than treatment prior to LT or interferon-treated recipients. Besides, most studies were from developed regions, including North American or European countries. Hence, multiregional studies are still needed to substantiate the comprehensive information for better clinical guidance globally. Finally, the field of HCV treatment is a dynamic and constantly changing landscape. A number of new agents or combination approaches may still in clinical trials or just licensed.

In summary, our results support DAAs as treatment for eradicating GT1 HCV recurrence in liver transplant recipients. They are highly effective and well-tolerated. However, fine-tuning is essential for achieving the optimal outcome, given considerations of drug availability, potential drug-drug interactions, the fibrotic or cirrhotic stage of the patients and regional/social factors.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHORS' CONTRIBUTIONS

QP conceived and designed the research, analyzed the data, performed statistical analysis, handled funding and supervision, drafted the article, and made critical revision of the article for important intellectual content. JL and BM conceived and designed the research, acquired the data, performed statistical analysis, drafted the article, and made critical revision of the article for important intellectual content. WC conceived and designed the research, acquired the data, and made critical revision of the article for important intellectual content. WB performed the literature research. ML acquired and analyzed the data, and made critical revision of the article for important intellectual content. MP conceived and designed the research, analyzed the data, performed statistical analysis, and made critical revision of the article for important intellectual content.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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