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Concise reviews

Real-World Effectiveness of Direct-Acting Antiviral Regimens against Hepatitis C Virus (HCV) Genotype 3 Infection: A Systematic Review and Meta-Analysis

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ABSTRACT

Patients with hepatitis C virus (HCV) genotype 3 (GT3) infection are resistant to direct-acting antiviral (DAA) treatments. This study aimed to analyze the effectiveness of sofosbuvir (SOF) + daclatasvir (DCV) ± ribavirin (RBV); SOF + velpatasvir (VEL) ± RBV; SOF + VEL + voxilaprevir (VOX); and glecaprevir (GLE) + pibrentasvir (PIB) in the treatment of HCV GT3-infected patients in real-world studies.

Articles were identified by searching the PubMed, EMBASE, and Cochrane Library databases from January 1, 2016 to September 10, 2019. The meta-analysis was conducted to determine the sustained virologic response (SVR) rate, using R 3.6.2 software.

Thirty-four studies, conducted on a total of 7328 patients from 22 countries, met the inclusion criteria. The pooled SVR rate after 12/24 weeks of treatment was 92.07% (95% CI: 90.39–93.61%) for the evaluated regimens. Also, the SVR rate was 91.17% (95% CI: 89.23–92.94%) in patients treated with SOF + DCV ± RBV; 95.08% (95% CI: 90.88–98.13%) in patients treated with SOF + VEL ± RBV; 84.97% (95% CI: 73.32–93.91%) in patients treated with SOF + VEL + VOX; and 98.54% (95% CI: 96.40–99.82%) in patients treated with GLE + PIB. The pooled SVR rate of the four regimens was 95.24% (95% CI: 93.50–96.75%) in non-cirrhotic patients and 89.39% (95% CI: 86.07–92.33%) in cirrhotic patients. The pooled SVR rate was 94.41% (95% CI: 92.02–96.42%) in treatment-naive patients and 87.98% (95% CI: 84.31–91.25%) in treatment-experienced patients.

The SVR rate of GLE + PIB was higher than other regimens. SOF + VEL + VOX can be used as a treatment regimen following DAA treatment failure.

1. Introduction

According to the reports of the World Health Organization (WHO), up to 71 million people were infected with the hepatitis C virus (HCV) around the world in 2015 [1]. The high rate of viral replication and mismatch in the process of replication leads to frequent viral mutations. The antiviral treatment regimen in the interferon era mainly included pegylated interferon, combined with ribavirin. However, this regimen had a low sustained virologic response (SVR) and was associated with more drug-related adverse events. With the clinical application of direct-acting antivirals (DAAs), the SVR rate significantly improved, and toxicity declined. However, previ-

Abbreviations: DAA, Direct-acting antiviral; DCV, Daclatasvir; EMA, the European Medicine Agency; FDA, the United States Food and Drug Administration; GLE, Glecaprevir; HCV, Hepatitis C virus; PIB, Pibrentasvir; RBV, Ribavirin; RASs, Resistance associated substitutions; SOF, Sofosbuvir; SVR, Sustained virologic response; VEL, Velpatasvir; VOX, Voxilaprevir; WHO, World Health Organization.

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ous studies have reported that the antiviral effectiveness of DAAs varies per genotype.

The SVR rate of HCV genotype 3 (GT3) infection is relatively lower than that of other genotypes. In recent years, considerable progress has been made in the antiviral treatment of HCV-GT3 infection, using new drug regimens and drug combinations. The United States Food and Drug Administration (FDA) and the European Medicine Agency (EMA) approved the regimens, containing sofosbuvir (SOF) + daclatasvir (DCV) ± ribavirin (RBV) in 2015 and SOF + velpatasvir (VEL) ± RBV in 2016 for the treatment of HCV-GT3 infection. They also approved SOF + VEL + voxilaprevir (VOX), as well as glecaprevir (GLE) + pibrentasvir (PIB), in 2017 [2].

In this meta-analysis, we systematically evaluated the pooled SVR rates of DAA regimens against HCV-GT3 infection in real-world studies.

2. Materials and methods

2.1. Literature search strategy

The following terms were used to search PubMed, EMBASE, and Cochrane Library from January 1, 2016 to September 10, 2019: ["sofosbuvir" AND "daclatasvir" OR "Sovaldi"] OR ["sofosbuvir" AND "velpatasvir" OR "Epclusa"] OR ["sofosbuvir" AND "velpatasvir" AND "voxilaprevir" OR "Vosevi"] OR ["glecaprevir" AND "pibrentasvir" OR "Mavyret"].

2.2. Inclusion and exclusion criteria

Two researchers (ZLW and ZY) scanned the titles and abstracts of the papers independently and assessed eligible trials, according to the inclusion criteria. Articles, which were potentially suitable based on the inclusion criteria, were extracted for a full-text review. Any disagreements were resolved by discussion. The inclusion criteria for the articles were as follows: subject (assessment of patients with chronic HCV infection); intervention (SOF + DCV, SOF + VEL, SOF + VEL + VOX, or GLE + PIB); primary outcomes (SVR rate after 12/24 weeks); and study design (real-world studies). On the other hand, the exclusion criteria were as follows: 1) unavailability of valid data related to HCV-GT3 infection; 2) inclusion of less than 10 patients in the study during treatment or follow-up for effectiveness evaluation; and 3) summaries, case reports, or meta-analyses.

2.3. Data extraction

Two authors (ZLW and ZY) read the full-text of articles independently. The information extracted from the articles included the demographics, main clinical characteristics of the patients, resistance-associated substitutions (RASs), average HCV RNA concentration at baseline, treatment regimen, drug dosage, therapy duration, SVR12/24, and virologic failure. Also, the authors resolved discrepancies by consultation with a third party (XHC).

2.4. Data analysis

Meta-analyses were conducted to determine the pooled SVR rate in all populations and subgroups, using the Freeman-Tukey double arcsine transformation in a random-effects model. Chi-square test was performed to compare the SVR rates of multiple groups. Also, Egger's test was conducted for evaluating potential publication bias. All analyses were performed in R 3.6.2 software with a meta package.

3. Results

3.1. Main characteristics of the studies and populations

A total of 7328 HCV GT3-infected patients were examined in 34 studies, which were selected among 5525 screened articles (Fig. 1). The studies were conducted in 22 countries: Germany (n = 6), Brazil (n = 4), USA (n = 3), France (n = 3), India (n = 3), Italy (n = 3), Pakistan (n = 3), Spain (n = 3), China (n = 2), Myanmar (n = 2), Norway (n = 2), Sweden (n = 2), Argentina(n = 1), Austria(n = 1), Denmark(n = 1), UK(n = 1), Finland(n = 1), Ireland(n = 1), Malaysia(n = 1), Netherlands(n = 1), Singapore(n = 1), and Thailand (n = 1). In 34 studies, there were 37 treatment regimens, of which 73% were SOF + DCV ± RBV (27/37, 73%), followed by SOF + VEL ± RBV (5/37, 14%), SOF + VEL + VOX (3/37, 8%), and GLE + PIB (2/37, 5%), respectively. The total number of patients included is 7328, 4701 patients were treated with SOF + DCV ± RBV (4701/7328, 64%), followed by SOF + VEL ± RBV (2266/7328, 31%), GLE + PIB (244/7328, 3%) and SOF + VEL + VOX (117/7328, 2%), respectively.

A summary of the demographic and clinical characteristics of the patients is presented in Table 1. Patients with chronic HCV-GT3 infection, included in these real-world studies, also had diseases, such as hepatitis and decompensated cirrhosis. Some of these patients had refractory comorbidities, such as hepatocellular carcinoma (HCC), HIV/HBV co-infection, renal failure, history of liver transplantation, and history of DAA treatment failure.

3.2. Pooled SVR rate for all patients

A total of 7328 patients with HCV-GT3 infection were treated with SOF + VEL + VOX, SOF + DCV ± RBV, SOF + VEL ± RBV, and GLE + PIB. The pooled SVR12/24 rate was 92.07% (95% CI: 90.39–93.61%), as shown in Fig. 2. The SVR12/24 rate was 84.97% (95% CI: 73.32–93.91%) in patients treated with SOF + VEL + VOX; 91.17% (95% CI: 89.23–92.94%) in patients treated with SOF + DCV ± RBV; 95.08% (95% CI: 90.88–98.13%) in patients treated with SOF + VEL ± RBV; and 98.54% (95% CI: 96.40–99.82%) in patients treated with GLE + PIB.

The results of Chi-square test indicated a significant difference in the SVR of four treatment regimens ($P < 0.001$). The two-by-two comparisons showed that GLE + PIB was superior to the other three regimens. The SOF + VEL ± RBV regimen was superior to SOF + VEL + VOX, which could be related to the selection of populations with a history of DAA (SOF + VEL or LDV or DCV or OBV/PTV-r + DSV) treatment failure in the SOF + VEL + VOX group. However, there was no significant difference between SOF + DCV ± RBV and SOF + VEL ± RBV or between SOF + DCV ± RBV and SOF + VEL + VOX.

3.3. Stratification analysis (non-cirrhotic patients)

According to the subgroup analysis of non-cirrhotic patients, the pooled SVR12/24 rate was 95.24% (95% CI: 93.50–96.75%) in patients treated with SOF + DCV ± RBV, SOF + VEL + VOX, and SOF + VEL ± RBV, as shown in Fig. 3A. The SVR12/24 rate was 95.36% (95% CI: 93.02–97.31%) in patients treated with SOF + DCV ± RBV; and 94.61% (95% CI: 89.78–98.00%) in patients treated with SOF + VEL ± RBV.

3.4. Stratification analysis (cirrhotic patients)

The pooled SVR12/24 rate was 89.39% (95% CI: 86.07–92.33%) in cirrhotic patients treated with SOF + DCV ± RBV, SOF + VEL + VOX, and SOF + VEL ± RBV, as shown in Fig. 3B. Based on the results, the SVR12/24 rate was 88.72% (95% CI: 85.19–91.86%) in patients

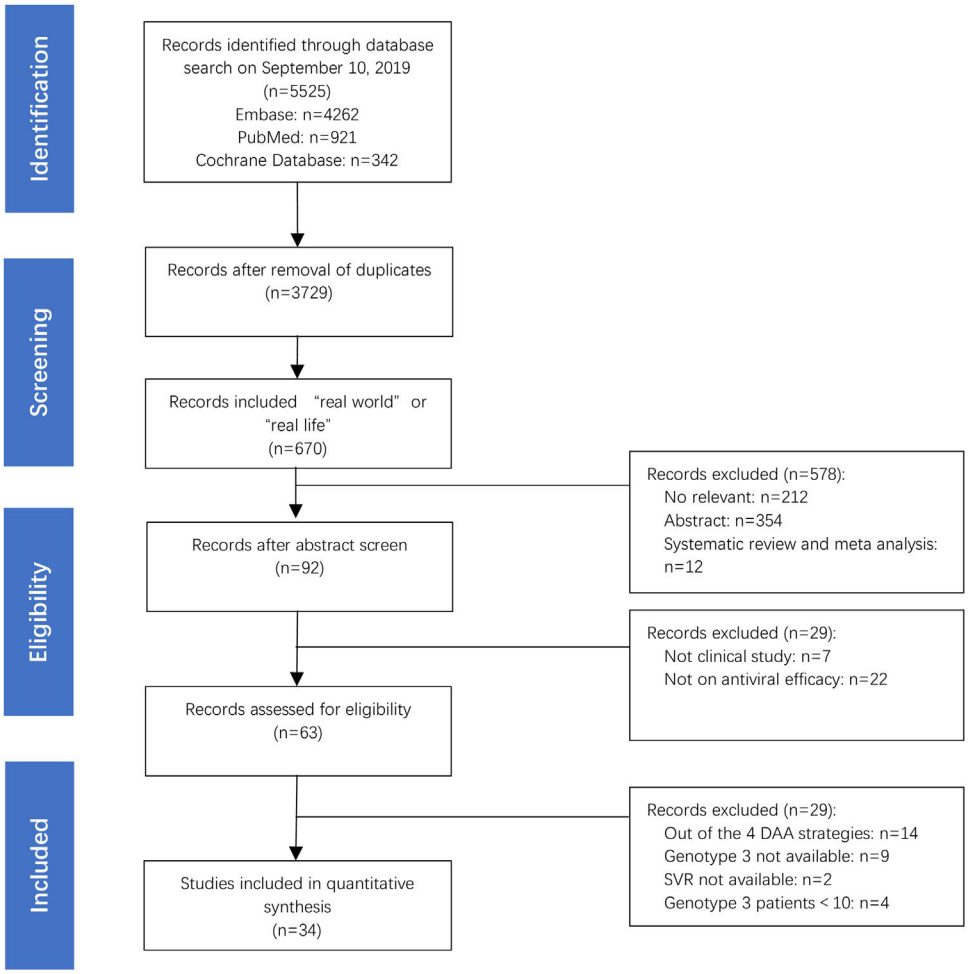

Fig. 1. The flowchart of article selection.

treated with SOF + DCV ± RBV; and 92.73% (95% CI: 81.85–99.03%) in patients treated with SOF + VEL ± RBV.

3.5. Stratification analysis (treatment-naive patients)

According to the subgroup analysis of treatment-naive patients, the pooled SVR12/24 rate in patients treated with SOF + DCV ± RBV and SOF + VEL ± RBV was 94.41% (95% CI: 92.02–96.42%), as shown in Fig. 3C. Also, the SVR rates in patients treated with SOF + DCV ± RBV and SOF + VEL ± RBV were 93.77% (95% CI: 90.15–96.65%) and 95.68% (95% CI: 90.73–98.87%), respectively.

3.6. Stratification analysis (treatment-experienced patients)

The pooled SVR12/24 rate of treatment-experienced patients with HCV-GT3 infection, treated with SOF + VEL + VOX, SOF + VEL ± RBV, and SOF + DCV ± RBV, was 87.98% (95% CI: 84.31–91.25%), as shown in Fig. 3D. Also, the corresponding SVR12/24 rates were 87.90% (95% CI: 72.16–98.02%), 90.24% (95% CI: 78.42–97.89%), and 86.25% (95% CI: 82.85–89.36%), respectively.

3.7. Sensitivity analysis of heterogeneity

Changes in the results of sensitivity analysis ranged from 91.75% to 92.39% after excluding articles one by one, which is a very small range, indicating stable results.

3.8. Publication bias

The results of Egger's test indicated no publication bias ($t = 0.12404$, DF = 35, P = 0.902), as shown in Fig. 4.

4. Discussion

In this review, the majority of treatment regimens in real-world studies included SOF + DCV ± RBV, which accounted for 73% of treatments. The SOF + DCV ± RBV regimen was the first-line therapeutic regimen for all HCV genotypes, as recommended by the FDA and EMA. In our meta-analysis, the pooled SVR12/24 was 91.17% in HCV GT3-infected patients. The SVR rates of cirrhotic and non-cirrhotic patients were 88.72% and 95.36%, respectively. Also, the SVR rates of treatment-experienced and treatment-naive patients were 86.25% and 93.77%, respectively.

The cirrhosis stage and history of treatment had significant effects on the antiviral effectiveness. In this regard, a phase III clinical study (ALLY-3) [37] showed that the pooled SVR12 rate of HCV GT3-infected patients, treated with SOF + DCV, was 89%, of which there was 63% in patients with cirrhosis and 96% in patients without cirrhosis; therefore, the SOF + DCV regimen was not suitable for cirrhotic and treatment-experienced patients with HCV-GT3 infection. Also, Amit Goel et al. [11] evaluated patients with renal insufficiency (eGFR<30 ml/min), treated with SOF (200 mg per day), and reported an SVR12 rate of 86.36%. Moreover, Mucenic et al. [22] selected patients with virologic relapse following liver transplantation and reported an SVR12 rate of 84.62%. Also, Carlos

Table 1
The main characteristics of studies included in the meta-analysis.

Study	Year	Country	Main clinical characteristics of the patients	Resistance-associated substitutions	Mean age	Sex (male/female)	Mean HCV RNA at baseline (log10 IU/mL)	No. of patients	Regimen and dosage	Treatment duration (weeks)	SVR12/24 (n)	Virologic failure[a](n)
Sarwar et al. [3]	2019	Pakistan	treatment experienced or with advanced fibrosis added RBV; with cirrhosis for 24 weeks; 58.4% with cirrhosis; 27.4% treatment experienced	NA	NA	NA	6.34	113	SOF (400 mg) + DCV (60 mg) ± RBV	12-24	102	NA
Pariente et al. [4]	2019	France	59.0% with cirrhosis	NA	NA	NA	NA	117	SOF (400 mg) + DCV (60 mg) ± RBV	12-24	103	NA
Mangia et al. [5]	2019	Italy	all with cirrhosis and portal hypertension, 54.1% transient elastography results >20 K Pa; 72.8% treatment naïve; 5.3% with HCC; 9.8% HIV positive; 14.6% past intravenous drug use; 18.5% alcohol abuse; 17.6% with diabetes	NA	52.9	175/30	2.53 ± 4.3	205	SOF (400 mg) + VEL (100 mg)	12	200	5 relapses
Macken et al. [6]	2019	England	91% with cirrhosis, 63.3% treatment naive	NA	NA	NA	NA	256	SOF (400 mg) + DCV (60 mg)±RBV	12	216	
Lobato et al. [7]	2019	Brazil	NA	NA	NA	NA	NA	817	SOF (400 mg) + DCV (60 mg)	12-24	736	NA
Llaneras et al. [8]	2019	Spain	all received a DAA-based interferon-free regimen: SOF and DCV or VEL or LDV; 43.3% with cirrhosis	of 6 relapses 1 detected with L28S, M31 L and D168 G, 1 with Y93H, 2 not detected, 2 NA	NA	NA	NA	30	SOF (400 mg) + VEL (100 mg) + VOX (100 mg)	12	24	6 relapses
Hlaing et al. [9]	2019	Myanmar	6.16% treatment experienced; 67.6% with cirrhosis or advanced fibrosis	NA	NA	NA	NA	193	SOF (400 mg) + DCV (60 mg) ± RBV	12-24	187	6 relapses

Table 1 (*Continued*)

Study	Year	Country	Main clinical characteristics of the patients	Resistance-associated substitutions	Mean age	Sex (male/female)	Mean HCV RNA at baseline (log10 IU/mL)	No. of patients	Regimen and dosage	Treatment duration (weeks)	SVR12/24 (n)	Virologic failure[a](n)
								83	SOF (400 mg) + VEL (100 mg)±RBV	12-24	75	8 relapses
Han et al. [10]	2019	China	62.5% with history of drug abuse; 25% with compensated cirrhosis; 9.4% renal impairment; 96.9% treatment naive	NA	44.26	26/6	5.91	32	SOF (400 mg) + DCV (60 mg)±RBV	12-24	31	1 relapse
Goel et al. [11]	2019	India	all eGFR<30 ml/min, 18.2% with cirrhosis;	NA	NA	NA	NA	22	SOF (200 mg) + DCV (60 mg)	12	19	0
Degasperi et al. [12]	2019	Italy	all with a prior DAA failure: SOF and VEL or LDV, or OBV/PTV-r + DSV	of 3 relapses 1 detected with Y93H, 2 NA	NA	NA	NA	42	SOF (400 mg) + VEL (100 mg) + VOX (100 mg) ± RBV	12	33	3 relapses
D'Ambrosio et al. [13]	2019	Italy	NA	of 2 relapses 1 detected with Y93H and L31I	NA	NA	NA	68	GLE (300 mg) + PIB (120 mg)	8-16	66	2 relapses
Butt et al. [14]	2019	Pakistan	84.2% treatment naïve, 52.5% with cirrhosis,	NA	47.06	33/68	NA	101	SOF (400 mg) + DCV (60 mg) ± RBV	24	96	NA
Berg et al. [15]	2019	Germany	8 weeks for treatment-naïve and non-cirrhotic patients, 12 weeks for treatment-naïve and cirrhotic patients, 16 weeks for treatment-experienced patients	NA	NA	NA	NA	176	GLE (300 mg) + PIB (120 mg)	8-16	174	NA
Belperio et al. [16]	2019	USA	42.1% with cirrhosis, 3.03% with HCC, 22.9% treatment experienced	NA	58.95	868/23	6.05	891	SOF (400 mg) + DCV (60 mg) ± RBV	12-16	796	NA

Table 1 (*Continued*)

Study	Year	Country	Main clinical characteristics of the patients	Resistance-associated substitutions	Mean age	Sex (male/female)	Mean HCV RNA at baseline (log10 IU/mL)	No. of patients	Regimen and dosage	Treatment duration (weeks)	SVR12/24 (n)	Virologic failure[a] (n)
			26.5% with cirrhosis, 2.42% with HCC, 9.7% treatment experienced		58.95	1662/73	6.05	1735	SOF (400 mg) + VEL (100 mg) ± RBV	12-24	1573	NA
Belperio et al. [17]	2019	USA	all treatment experienced: SOF and DCV or VEL or LDV, 51.1% with cirrhosis, 4.44% with HCC, 2.22% with HIV coinfected, 37.8% with diabetes	NA	59.7	51/0	6.1	45	SOF (400 mg) + VEL (100 mg) + VOX (100 mg)	12	42	NA
Araujo et al. [18]	2019	Brazil	6.5% with cirrhosis	NA	NA	NA	NA	31	SOF (400 mg) + DCV (60 mg)	12	30	1 virologic failure
Wehmeyer et al. [19]	2018	Germany	28.75% treatment experienced, 33.75% with cirrhosis, 15% with HIV coinfected	NA	NA	NA	NA	80	SOF (400 mg) + DCV (60 mg) ± RBV	12-24	76	NA
Felden et al. [20]	2018	Germany	24.8% treatment experienced, 26.6% with cirrhosis, 8.56% with HIV coinfected	22 patients with baseline NS5A RASs (Y93H, A30 K or L31 M)	NA	NA	NA	222	SOF (400 mg) + VEL (100 mg) ± RBV	12	213	NA
Tao et al. [21]	2018	China	34.6% with cirrhosis	NA	41.71	48/33	6.30	81	SOF (400 mg) + DCV (60 mg) ± RBV	12-24	71	10 relapses
			23.8% with cirrhosis		37.38	13/8	6.04	21	SOF (400 mg) + VEL (100 mg)	12-24	21	0
Mucenic et al. [22]	2018	Brazil	all liver transplant recipients	NA	NA	NA	NA	26	SOF (400 mg) + DCV (60 mg) ± RBV	12	22	2 relapses and 2 non-responses

Table 1 (*Continued*)

Study	Year	Country	Main clinical characteristics of the patients	Resistance-associated substitutions	Mean age	Sex (male/female)	Mean HCV RNA at baseline (log10 IU/mL)	No. of patients	Regimen and dosage	Treatment duration (weeks)	SVR12/24 (n)	Virologic failure[a] (n)
Minguez et al. [23]	2018	Spain	all HIV-coinfected	NA	NA	NA	NA	53	SOF (400 mg) + DCV (60 mg) ± RBV	12	48	
Mehta et al. [24]	2018	India	NA	NA	NA	NA	NA	372	SOF (400 mg) + DCV (60 mg) ± RBV	12-24	362	5 non-responses, 2 break-throughs, and 10 relapses
Marciano et al. [25]	2018	Argentina	89.4% with cirrhosis,	NA	NA	NA	NA	47	SOF (400 mg) + DCV (60 mg) ± RBV	24	38	NA
Lim et al. [26]	2018	India, Myanmar, Pakistan, Thailand, Singapore, and Malaysia	NA	NA	NA	NA	NA	310	SOF (400 mg) + DCV (60 mg) ± RBV	12-24	282	6
Kwo et al. [27]	2018	USA	64% liver transplant, 36% with decompensated cirrhosis	NA	NA	NA	NA	25	SOF (400 mg) + DCV (60 mg) ± RBV	24	22	1 breakthrough
Rockstroh et al. [28]	2017	Germany	all HIV-coinfected and with an advanced stage of cirrhosis	NA	NA	NA	NA	13	SOF (400 mg) + DCV (60 mg) ± RBV	24	12	NA
Lacombe et al. [29]	2017	France	all HIV-coinfected and with advanced liver disease	NA	NA	NA	NA	47	SOF (400 mg) + DCV (60 mg) ± RBV	12-24	42	2 relapses and 1 undefined virologic failure

Table 1 (*Continued*)

Study	Year	Country	Main clinical characteristics of the patients	Resistance-associated substitutions	Mean age	Sex (male/female)	Mean HCV RNA at baseline (log10 IU/mL)	No. of patients	Regimen and dosage	Treatment duration (weeks)	SVR12/24 (n)	Virologic failure[a](n)
Hezode et al. [30]	2017	France	76.9% with cirrhosis, 8.1% with HCC, 9.0% post-liver transplant HCV recurrence, 9.0% pre-liver/renal transplant, 71.2% treatment experienced, 14.1% HIV-coinfected, 2.1% HBV-coinfected	NA	54.2	245/88	6.0	333	SOF (400 mg) + DCV (60 mg) ± RBV	12-24	278	4 break-throughs, 32 relapses, and 9 undefined
Dalgard et al. [31]	2017	Denmark, Sweden, Norway, and Finland	51.8% treatment experienced, 73.2% with cirrhosis	NA	56	135/60	NA	193	SOF (400 mg) + DCV (60 mg) ± RBV	12-24	177	NA
Cornberg et al. [32]	2017	Germany	32.7% with cirrhosis, 29.1% treatment experienced	NA	NA	NA	NA	220	SOF (400 mg) + DCV (60 mg)±RBV	12-24	207	NA
Gray et al. [33]	2017	Ireland	28.9% treatment experienced	NA	NA	NA	NA	76	SOF (400 mg) + DCV (60 mg) ± RBV	24	67	0
Sette-Jr et al. [34]	2017	Brazil	35.7% with cirrhosis	of 4 relapses 2 detected with Y93H, 2 not done	NA	NA	NA	28	SOF (400 mg) + DCV (60 mg) ± RBV	12-24	24	4 relapses
Alonso et al. [35]	2017	Spain	26% with decompensated cirrhosis, 45% treatment experienced	NA	55	110/21	6.0	131	SOF (400 mg) + DCV (60 mg) ± RBV	12-24	123	6 relapses, 1 breakthrough
Welzel et al. [36]	2016	Germany, Austria, Netherlands, Sweden, and Norway	84.9% with cirrhosis, 60.2% treatment experienced	NA	NA	NA	NA	93	SOF (400 mg) + DCV (60 mg) ± RBV	24	82	NA

NA: Data not available for HCV GT3-infected patients; DSV: Dasabuvir; LDV: Ledipasvir; OBV/PTV-r: Ombitasvir/paritaprevir-ritonavir; VEL: Velpatasvir.

[a] Relapse or breakthrough or undefined virologic failure.

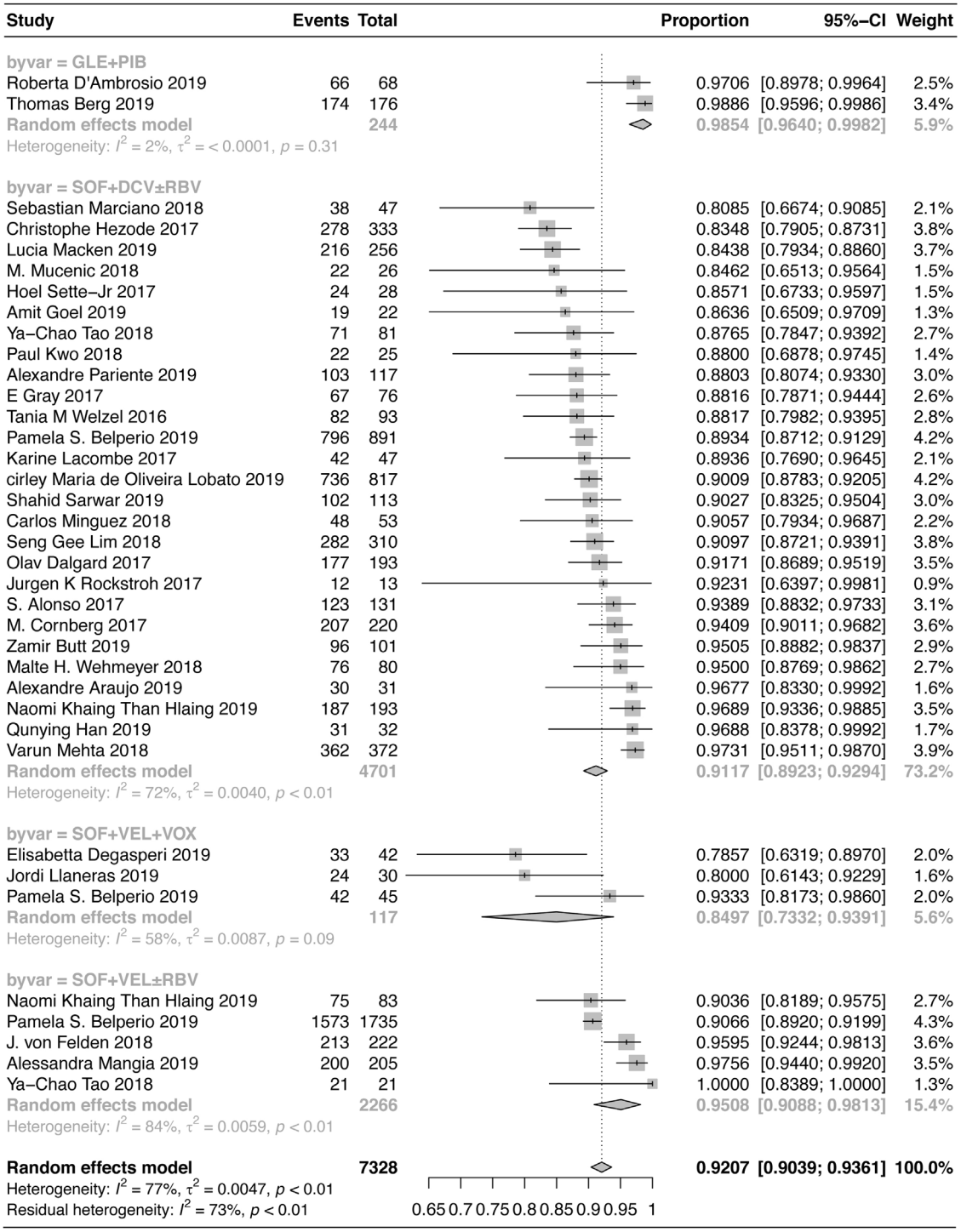

Fig. 2. The forest plots of pooled SVR rates for all patients.

Minguez [23], Jurgen K Rockstroh [28], and Karine Lacombe [29] in studies on HIV co-infected patients reported SVR rates of 90.57%, 92.31%, and 89.36%, respectively. Compared to renal insufficiency and virologic relapse following liver transplantation, the effect of HIV co-infection on the antiviral effectiveness of SOF + DCV ± RBV was relatively less significant.

The SOF + VEL ± RBV regimen, approved in 2017, is the first treatment regimen, which can be used for 12 weeks, regardless of HCV genotype and liver fibrosis stage. In the present study, the SVR rate of patients with HCV-GT3 infection was 95.08%, which is higher than that of SOF + DCV ± RBV. The SVR rates of cirrhotic, non-cirrhotic, treatment-naive, and treatment-experienced patients, treated with SOF + VEL ± RBV, were 92.73%, 94.61%, 95.68%, and 90.24%, respectively. The effect of treatment history on the antiviral effectiveness of SOF + VEL ± RBV was more significant than that of cirrhosis stage.

Belperio et al [16] gained the similar SVR rates of the GT3 HCV patients treated with SOF + VEL ± RBV compared with SOF + DCV ± RBV. In this meta-analysis the pooled SVR rate of SOF + VEL ± RBV was a little higher (95.08%) than that of SOF + DCV ± RBV (91.17%). This may be associated with the high SVR rate (100%, 21/21) from Tao's study [21]. In non-cirrhotic patients,

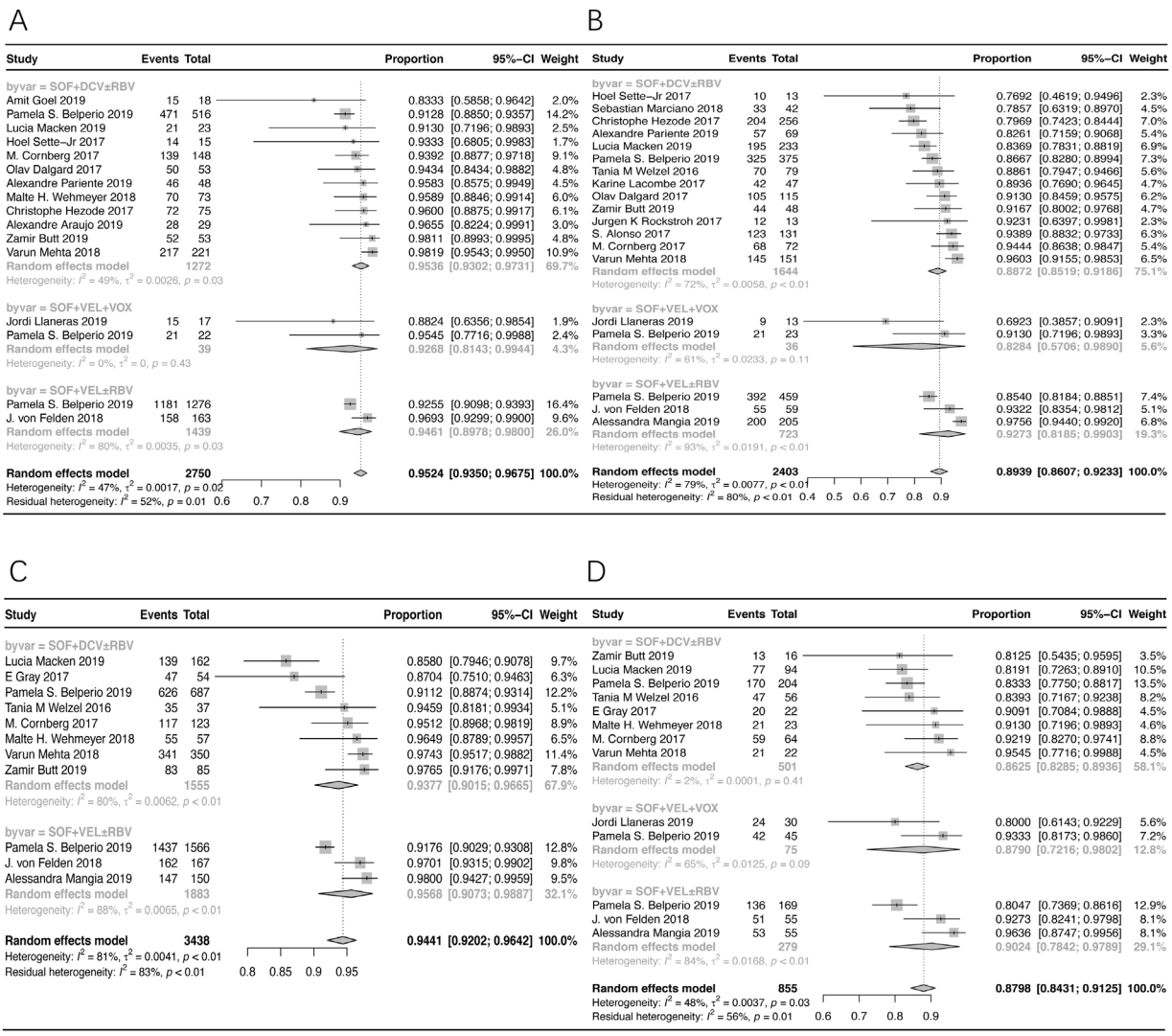

Fig. 3. The forest plots of stratification analysis. (A) The forest plots of SVR rates in non-cirrhotic patients. (B) The forest plots of SVR rates in cirrhotic patients. (C) The forest plots of SVR rates in treatment-naive patients. (D) The forest plots of SVR rates in treatment-experienced patients.

the SVR rates of the two regimens were almost the same (94.61% for SOF + VEL ± RBV and 95.36% for SOF + DCV ± RBV). However, in patients with cirrhosis, the SVR rate of SOF + VEL ± RBV was higher than that of SOF + DCV ± RBV (92.73% and 88.72%, respectively). Also, in cirrhotic patients, the SOF + VEL ± RBV regimen was found to be more suitable than SOF + DCV ± RBV.

The GLE + PIB regimen was approved by the FDA and EMA, regardless of HCV genotypes. This regimen decreases the treatment duration to eight weeks for hepatitis and compensated cirrhotic patients. It can be also used for patients with renal dysfunction or even those undergoing dialysis. In a phase-III clinical study (ENDURANCE-3) [38] on patients treated with GLE + PIB for 8 or 12 weeks, the SVR rate was 95% in treatment-naive hepatitis patients with HCV-GT3 infection. Also, in the SURVEYOR-II Part-3 study [39], the SVR rate of HCV GT3-infected patients was 91% after 12 weeks of treatment; the patients were either treatment-naive or treatment-experienced, with or without cirrhosis. Moreover, in the EXPEDITION-2,4 studies [40,41], the SVR rate was 98% in patients after 8-12 weeks of treatment. In this real-world meta-analysis, the SVR rate of patients with HCV-GT3 infection, treated with GLE + PIB, could reach 97% or higher.

Our meta-analysis showed that the SVR rate of SOF + VEL + VOX was 84.97%, which is lower than that of SOF + DCV ± RBV,

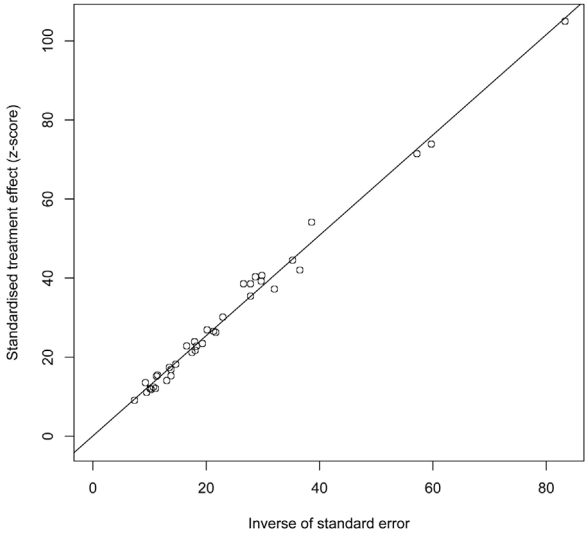

Fig. 4. The funnel plot.

SOF + VEL ± RBV, and GLE + PIB; this result may be related to previous resistance to DAA (SOF + VEL or LDV or DCV or OBV/PTV-r + DSV) in patients treated with SOF + VEL + VOX. The SOF + VEL + VOX regimen, which included a combination of three DAAs, was mainly designed as a treatment plan for patients with a history of DAA treatment failure. In this regard, the POLARIS-3 study [42] evaluated patients with liver cirrhosis, who were initially treated with DAAs. After eight weeks of treatment with SOF + VEL + VOX, the SVR rate of patients with HCV-GT3 infection reached 96% (106/110).

Moreover, in the POLARIS-1 study [43], the SVR rate of patients with HCV-GT3 infection was 95% (74/78) after 12 weeks of treatment. In this paper, some real-world studies [8,12,17] on patients with a history of DAA treatment failure reported SVR rates of 80.00%, 78.57%, and 93.33%, respectively. The antiviral effectiveness of SOF + VEL + VOX in real-word studies was lower than that of registered clinical studies in patients with a history of DAA treatment failure. Also, in two real-word studies [8,12], the number of patients with virologic relapse was 6/30 and 3/42 during the follow-up, respectively.

In real-world studies, the SVR rate of SOF + VEL + VOX was low in HCV GT3-infected patients with a history of DAA treatment failure, and the possibility of virologic relapse was still high. Overall, HCV-GT3 infection in patients with a history of DAA treatment failure poses challenges for the current antiviral treatments. In the present study, the pooled SVR rate of the four antiviral regimens for HCV-GT3 infection was 92.07%. The SVR rate of GLE + PIB was the highest (98.54%), and the treatment duration was the shortest (possibly eight weeks).

Clinical trials [37,44] reported that patients with the presence of baseline RASs (Y93H and A30 K) in the NS5A gene had lower SVR rates, which was associated with decreased in vitro activity of DCV and VEL. In the ASTRAL-3 study [45], 84% SVR in the presence of Y93H compared to 97% in patients without Y93H was achieved from patients treated with SOF/VEL. However, in this meta-analysis only 6 articles completed RAVs test. It is interesting that all the 6 studies [8,12,13,17,20,34] draw a conclusion that RASs may be not associated with lower SVR rate. High SVR rates in patients completing therapy suggested that pretreatment RAS testing may not be necessary.

This meta-analysis has limitations. We think that no strong conclusions can be drawn due to high heterogeneity in four DAA regimens administration in real-world setting from 22 countries, as well as small numbers of patients treated with SOF + VEL + VOX and GLE + PIB. More studies are needed in the future in order to better analyze the antiviral effectiveness of DAAs in GT3 HCV patients in real-world studies.

5. Conclusion

According to our meta-analysis of real-world studies, the antiviral effectiveness of treatment regimens for HCV-GT3 infection, including SOF + DCV ± RBV, SOF + VEL ± RBV, GLE + PIB, and SOF + VEL + VOX, was good. The SVR rate of GLE + PIB was higher, and the treatment duration was shorter than other regimens. Based on the findings, SOF + VEL + VOX can be used as a treatment regimen following DAA treatment failure. Also, a history of DAA treatment failure still poses challenges for current treatments.

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Conflict of interest

All authors had approved the final version of the manuscript for publication and agreed to be accountable for all aspects of the work. The authors have read the journal's policy on conflicts of interest and they declare that they have no competing interest.

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