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© 2025 Zhuang, Li, Zhang, Ji and Xing. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms. Real-world effectiveness of sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, and sofosbuvir/velpatasvir/ voxilaprevir against genotype 3 hepatitis C virus infection: a systematic review and meta-analysis

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Introduction: Direct antiviral agents (DAAs) have dramatically changed the landscape of liver diseases associated with chronic hepatitis C virus (HCV) infection. However, limited data are available on the antiviral effect of sofosbuvir (SOF) + velpatasvir (VEL) \pm ribavirin (RBV), SOF + VEL + voxilaprevir (VOX), and glecaprevir (GLE) + pibrentasvir (PIB) in treating patients infected with HCV GT3 in a real-world setting.

Methods: Using the EMBASE, PubMed, and Cochrane Library databases, articles were screened from 1 January 2016 to 1 June 2024. The sustained virologic response (SVR) rates were analyzed using the Freeman–Tukey double arcsine transformation in a random-effects model in R4.1.0 software.

Results: We recruited 3,177 patients with HCV GT3 in 19 studies from 9 countries. The pooled SVR12/24 rate of the three evaluated regimens was 94.00% (95% CI: 90.87-96.59%). Furthermore, the SVR rate was 83.81% (95% CI: 75.70-90.62%) in patients receiving SOF+VEL+VOX; 94.98% (95% CI: 92.02-97.33%) in patients receiving SOF+VEL \pm RBV; and 96.96% (95% CI: 93.20-99.45%) in patients receiving GLE+PIB. The pooled SVR12/24 rate of the three regimens was 95.70% (95% CI: 91.74-98.58%) and 90.50% (95% CI: 83.50-95.90%) in non-cirrhotic and cirrhotic patients, respectively. The pooled SVR rate was 96.79% (95% CI: 93.37-99.13%) and 88.41% (95% CI: 82.67-93.22%) in treatment-naive and treatment-experienced patients, respectively.

Conclusion: SOF+VEL \pm RBV, GLE+PIB, and SOF+VEL+VOX had good antiviral effectiveness for chronic HCV-GT3 infection in real-world settings. Factors such as cirrhosis and treatment experience, especially previous DAA treatment failure, may influence the SVR rate.

KEYWORDS

real-world effectiveness, sofosbuvir/velpatasvir, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir/voxilaprevir, genotype 3 HCV

Introduction

Approximately 58 million individuals have been infected by the hepatitis C virus (HCV) in the world and 290,000 patients died from diseases associated with HCV in 2019 (1). A worldwide health sector strategy to eliminate HCV by 2030 was proposed by the World Health Organization(WHO)6 years ago (2). The sustained virologic response (SVR) has been improved significantly with the clinical application of direct-acting antivirals (DAAs) in recent years (3-9). It is reported that SVR rates of different DAAs are variable depending on the HCV genotype (GT), especially genotype 3 (10-12). Significant progress in the inhibition of HCV replication has been achieved by using new drug regimens and drug combinations such as sofosbuvir (SOF) + velpatasvir (VEL) ± ribavirin (RBV) in 2016 and SOF + VEL + voxilaprevir (VOX) and glecaprevir (GLE) + pibrentasvir (PIB) in 2017, which were approved by the European Medicine Agency (EMA) or the United States Food and Drug Administration (FDA) (13).

The antiviral effectiveness of DAAs may be decreased in a realworld setting because of poor compliance and the population diversity of patients (14–17). There is a dearth of analysis on the antiviral effectiveness of SOF+VEL \pm RBV, SOF+VEL+VOX, and GLE+PIB in a real-world setting.

Thus, to evaluate the pooled SVR rate against HCV-GT3 infection in a real-world setting, we systematically searched and analyzed the latest data on SOF+VEL \pm RBV, SOF+VEL+VOX, and GLE+PIB.

Methods

Literature search method

Using EMBASE, PubMed, and Cochrane Library, studies were searched for from 1 January 2016 to 1 June 2024 using the following terms: ("Epclusa" OR "velpatasvir" AND "sofosbuvir") OR ("Mavyret" OR "pibrentasvir" AND "glecaprevir") OR ("Vosevi" OR "voxilaprevir" AND "velpatasvir" AND "sofosbuvir").

Inclusion and exclusion criteria

Two independent researchers screened the abstracts and titles of potentially eligible publications. A full-text review of the selected articles was then performed for advanced selection in accordance with the criteria for inclusion and exclusion. Objections were discussed and resolved with a third party. The criteria for inclusion were: subject (patients infected with HCV GT3 chronically); intervention (SOF+VEL± RBV, GLE+PIB, or SOF +VEL+VOX); primary outcome (SVR rate after 8-24 weeks); and study design (real-world study). The following exclusion criteria were used: A) inaccessibility of valid data on HCV-GT3; B) assessing fewer than 10 cases; and C) meta-analyses, summaries, or case reports.

Data extraction

Two authors independently extracted the data. Data on the demographics, SVR12, therapy duration, average HCV RNA concentration at baseline, drug dosage, treatment regimen, and virological failure were extracted using standardized forms from the articles.

Data analysis

The SVR rates were analyzed using the Freeman–Tukey double arcsine transformation in a random-effects model. Furthermore, Egger's test assessed publication bias, and the data analysis was conducted using R4.4.1 software. The output results do not involve ethical issues, and the research was exempted from ethical review by the Ethics Committee.

Results

Main characteristics of the populations and studies

Overall, 3,177 HCV GT3-infected individuals were recruited in the 19 included articles, selected from a total of 3443 articles step by step as shown in Figure 1. These studies were conducted in eight countries: Italy (n=4), the USA (n=4), China (n=3), Germany (n=2), Japan (n=2), Denmark (n=1), Myanmar (n=1), Spain (n=1), and the UK(n=1). Of the studies, 42.11% were on GLE +PIB (8/19), 36.84% on SOF+VEL \pm RBV (7/19), and 21.05% on SOF+VEL+VOX (4/19), as presented in Figure 2.

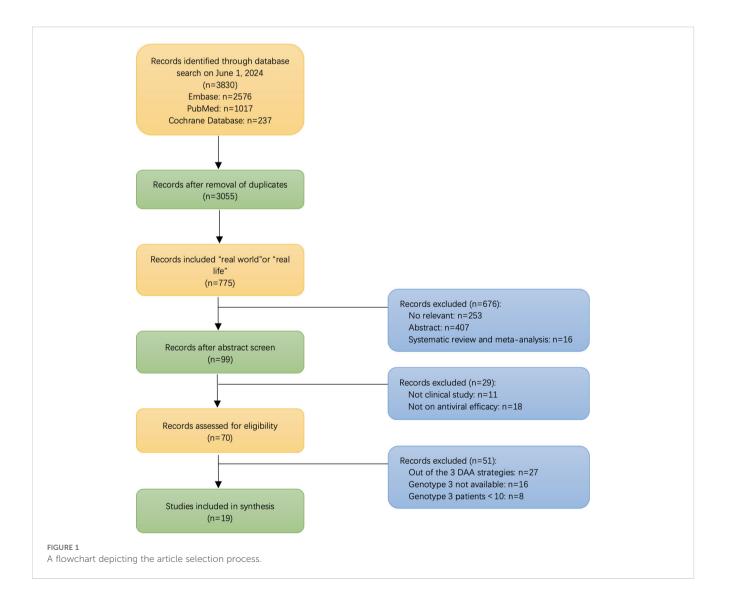
The patients' clinical and demographic characteristics are shown in Table 1. The stages of liver disease in the patients infected by genotype 3 HCV included in these real-world studies ranged from hepatitis, advanced fibrosis, and compensated cirrhosis to decompensated cirrhosis. Some patients had at least one of the following refractory comorbidities: HIV/HBV coinfection, hepatocellular carcinoma (HCC), diabetes, history of liver transplantation, renal failure, alcohol abuse, intravenous drug use, and history of previous DAA treatment failure.

Pooled SVR rate for all cases

The pooled SVR12/24 rate for cases that received SOF+VEL +VOX, SOF+VEL \pm RBV, and GLE+PIB was 94.00% (95% CI: 90.87-96.59%) (Figure 3). In addition, the SVR12/24 rate was 83.81% (95% CI: 75.70-90.62%) in cases that received SOF+VEL +VOX, 94.98% (95% CI: 92.02-97.33%) in cases that received SOF +VEL \pm RBV, and 96.96% (95% CI: 93.20-99.45%) in cases that received GLE+PIB.

Stratification assessment of noncirrhotic cases

The subgroup assessment of non-cirrhotic cases showed that the pooled SVR12/24 rate was 95.70% (95% CI: 91.74-98.58%) in



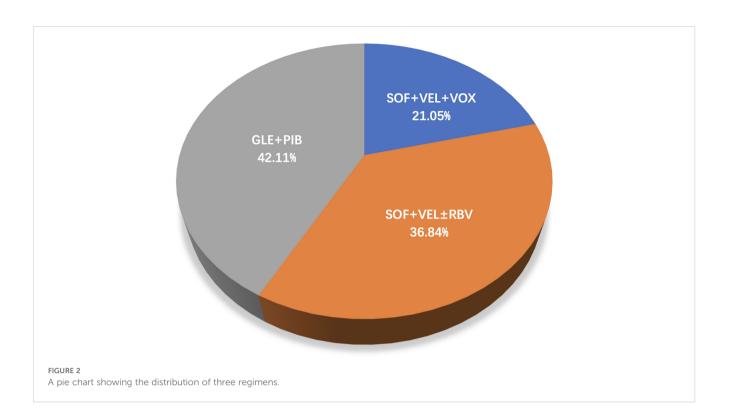


TABLE 1 The demographic characteristics of the patients.

Author, Year	Region	Sample size	Pre-treat- ment HCV RNA (log10 IU/mL)	Age (years)	Male, No. (%)	Demographic characteristics	Regimen, duration (weeks)	SVR12/ 24, No.	Virological failure*
Mangia et al., 2019 (18)	Italy	205	2.53 ± 4.3	52.9	175 (85.3)	72.8% treatment naïve; 54.1% transient elastography results >20KPa; 18.5% alcohol abuse; 17.6% with diabetes; 14.6% past intravenous drug use; 9.8% HIV positive; 5.3% with HCC; all with cirrhosis.	SOF +VEL, 12	200	5
Llaneras et al., 2019 (19)	Spain	30	NA	NA	NA	43.3% with cirrhosis; all treated with DCV and SOF or LDV or VEL.	SOF+VEL +VOX, 12	24	6
Hlaing et al., 2019 (20)	Myanmar	83	NA	NA	NA	67.6% with cirrhosis or advanced fibrosis; 6.16% treatment- experienced: Peg-IFN or DAA-based.	SOF+VEL ± RBV, 12-24	75	8
Degasperi et al., 2019 (21)	Italy	42	NA	NA	NA	All failed with OBV/PTV-r + DSV, or SOF and LDV or VEL	SOF+VEL +VOX ± RBV, 12	33	3
D'Ambrosio et al., 2019 (22)	Italy	68	NA	NA	NA	NA	GLE+PIB, 8-16	66	2
Berg et al., 2019 (23)	Germany	176	NA	NA	NA	Non-cirrhotic and treatment- naïve patients treated for 8 weeks, 12 were cirrhotic and treatment- naïve, 16 were treatment-experienced.	GLE+PIB, 8-16	174	NA

(Continued)

TABLE 1 Continued

Author, Year	Region	Sample size	Pre-treat- ment HCV RNA (log10 IU/mL)	Age (years)	Male, No. (%)	Demographic characteristics	Regimen, duration (weeks)	SVR12/ 24, No.	Virological failure*
Belperio et al., 2019 (24)	USA	1735	6.05	58.95	1662 (95.8)	26.5% with cirrhosis; 9.7% treatment experienced: SOF/LDV ± RBV, PegIFN+RBV, SOF+ PegIFN+RBV, SOF+RBV;2.42% with HCC.	SOF+VEL ± RBV, 12-24	1573	NA
Belperio et al., 2019 (25)	USA	45	6.1	59.7	NA	51.1% with cirrhosis; 37.8% with diabetes; 4.44% with HCC; 2.22% with HIV coinfected; all treated with DCV and SOF or LDV or VEL.	SOF+VEL +VOX, 12	42	NA
Felden et al., 2018 (26)	Germany	222	NA	NA	NA	26.6% with cirrhosis; 24.8% treatment-experienced: Peg-IFN ± RBV or DAA-based; 8.56% with HIV coinfected.	SOF+VEL ± RBV, 12	213	NA
Tao et al., 2018 (27)	China	21	6.04	37.38	13 (59.3)	23.8% with cirrhosis.	SOF+VEL, 12-24	21	0
Mangia et al., 2019 (28)	Italy	204	NA	NA	NA	57.4% with F3-F4 stage; 43.14% PWID; 42.6% with F0-F2; 12.25% with ribavirin.	SOF+VEL ± RBV, 12	198	NA
Toyoda et al., 2020 (29)	Japan	14	6.5	46	6 (42.9)	42.9% with cirrhosis; 28.6% with HCC; 21.4% DAA-experienced: DAA-based.	GLE +PIB, 12	13	1
Nozaki et al., 2020 (30)	Japan	20	NA	54	9 (45.0)	75.0% treatment-naïve; 30.0% with cirrhosis; 30.0% with HCC; 25.0% treated by SOF/RBV or DCV/ASV.	GLE +PIB, 12	16	4
Smith et al., 2021 (31)	UK	62	6.4	57	53 (85.5)	59.67% with cirrhosis; 14.5% with prior liver transplant;12.9% with HCC; all with previous DAA treatment failure.	SOF+VEL +VOX, 8-24	50	NA
Chen et al., 2021 (32)	China Taiwan	86	NA	NA	NA	87.21% treatment-naïve; 79.07% without cirrhosis;20.93% with cirrhosis; 12.79% treatment-experienced.	GLE+PIB, 8-16	82	NA
Curry et al., 2021 (33)	USA	57	NA	43	22 (38.6)	23% CKD Stage 1-3; 5% CKD Stage 4-5;all treatment-naïve and non-cirrhotic.	GLE +PIB, 8	57	0
Solomon et al., 2022 (34)	USA	80	NA	43	NA	All treatment-naïve.	SOF +VEL, 12	73	NA
Madsen et al., 2022 (35)	Denmark	11	NA	NA	NA	All treatment-naïve and without significant liver fibrosis.	GLE+PIB, 4-8	10	NA
Chang et al., 2021 (36)	China Taiwan	11	NA	NA	NA	All treatment-naïve.	GLE +PIB, 8	11	NA

 * denotes a relapse or break through or undefined virological failure.

cases that received GLE+PIB, SOF+VEL+VOX, and SOF+VEL \pm RBV (Figure 4A). Moreover, the SVR12/24 rate was 95.91% (95% CI: 83.38-100%) in cases that received GLE+PIB, 92.68% (95% CI: 81.43-99.44%) in cases that received SOF+VEL+VOX, and 94.61% (95% CI: 89.78-98.00%) in cases that received SOF+VEL \pm RBV.

Stratification assessment of cirrhotic cases

The pooled SVR12/24 rate was 90.50% (95% CI: 83.50-95.90%) in cirrhotic patients treated with GLE+PIB, SOF+VEL+VOX, and SOF+VEL \pm RBV (Figure 4B). The SVR12/24 rate was 91.10% (95%

Study	Events	Total		Proportion	95%-CI	Weight
SOF+VEL±RBV			_			
Alessandra Mangia 2019	200				[0.9440; 0.9920]	
Naomi Khaing Than Hlaing 20					[0.8189; 0.9575]	
Pamela S. Belperio 2019		1735	· · ·		[0.8920; 0.9199]	
J. von Felden 2018	213				[0.9244; 0.9813]	
Ya–Chao Tao 2018	21	21			[0.8389; 1.0000]	
Alessandra Mangia 2019	198				[0.9371; 0.9891]	
Sunil S Solomon 2022	73				[0.8280; 0.9641]	
Random effects model		2550	\diamond	0.9498	[0.9202; 0.9733]	44.6%
Heterogeneity: $I^2 = 82\%$, $\tau^2 = 0.00$	41, <i>p</i> < 0.01					
SOF+VEL+VOX			_			
Jordi Llaneras 2019	24		,		[0.6143; 0.9229]	
Elisabetta Degasperi 2019	33	. —			[0.6319; 0.8970]	
Pamela S. Belperio 2019	42				[0.8173; 0.9860]	
David A. Smith 2021	50				[0.6863; 0.8958]	
Random effects model		179		0.8381	[0.7570; 0.9062]	19.9%
Heterogeneity: $I^2 = 43\%$, $\tau^2 = 0.00$	43, <i>p</i> = 0.16					
GLE+PIB			_			
Roberta D'Ambrosio 2019	66				[0.8978; 0.9964]	
Thomas Berg 2019	174				[0.9219; 0.9843]	
Hidenori Toyoda 2020	13				[0.6613; 0.9982]	
Akito Nozaki 2020	16		•		[0.5634; 0.9427]	3.5%
Chi-Yi Chen 2021	82				[0.8852; 0.9872]	
Michael P. Curry 2021	57				[0.9373; 1.0000]	
Lone W. Madsen 2022	10				[0.5872; 0.9977]	
Kao-Chi Chang 2021	11	11			[0.7151; 1.0000]	
Random effects model Heterogeneity: $l^2 = 46\%$, $\tau^2 = 0.00$	50, <i>p</i> = 0.08	448	\diamond	0.9696	[0.9320; 0.9945]	35.5%
Random effects model		3177	\diamond	0.9400	[0.9087; 0.9659]	100.0%
Heterogeneity: $I^2 = 77\%$, $\tau^2 = 0.00$	98, <i>p</i> < 0.01	Г				
Test for subgroup differences: χ^2_2 =			0.7 0.8 0.9 1			

FIGURE 3

The forest plots of the pooled SVR rates for all patients.

A										
Study	Events Total		Proportion 95%-	-CI Weight	Study	Events Total		Proportion	95%-CI	Weight
SOF+VEL+VOX					SOF+VEL±RBV					
Jordi Llaneras 2019	15 17		0.8824 [0.6356; 0.985		Alessandra Mangia 2019	200 205			9440; 0.9920]	18.5%
Pamela S. Belperio 2019			0.9545 [0.7716; 0.998		Pamela S. Belperio 2019	180 208			3114; 0.9086]	18.5%
Random effects model	39		0.9268 [0.8143; 0.994	14] 16.0%	Pamela S. Belperio 2019	212 251			7938; 0.8871]	18.8%
Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0\%$	0, p = 0.43				J. von Felden 2018 Random effects model	55 59 723				15.2% 71.0%
SOF+VEL±RBV Pamela S. Belperio 2019	4404 4070		0.9255 [0.9098; 0.939	001 05 00/	Heterogeneity: $I^2 = 90\%$, $\tau^2 =$	0.0136, <i>p</i> < 0.0	1			
J. von Felden 2018	158 163		0.9693 [0.9299; 0.990		SOF+VEL+VOX					
Random effects model	1439	-	0.9461 [0.8978; 0.980		Jordi Llaneras 2019	9 13		0.6000 10.	3857; 0.9091]	8.2%
Heterogeneity: $l^2 = 80\%$, τ^2 :		<u> </u>	0.5401 [0.6576, 0.560	10] 40.0 %	Pamela S. Belperio 2019	21 23				11.0%
Heterogeneity: $T = 60\%$, τ	= 0.0035, <i>p</i> = 0.03				Random effects model	21 25	ini		706; 0.9890]	
GLE+PIB					Heterogeneity: $I^2 = 61\%$, $\tau^2 =$		1	0.0204 [0.4	100, 0.3030]	10.2.70
Akito Nozaki 2020	11 14		0.7857 [0.4920; 0.953	34] 6.4%	Heterogenengt / = er /a, t =	0.0200, p = 0.1				
Chi-Yi Chen 2021	65 68	-	- 0.9559 [0.8764; 0.990		GLE+PIB					
Michael P. Curry 2021	57 57	<u> </u>	1.0000 [0.9373; 1.000		Chi-Yi Chen 2021	17 18		0.9444 [0]	7271; 0.9986]	9.8%
Random effects model	139		 0.9591 [0.8338; 1.000 		Random effects model	18			768; 1.0000]	9.8%
Heterogeneity: $l^2 = 79\%$, τ^2 :			0.0001 [0.0000] 11000	01 0111/0	Heterogeneity: not applicable					
Random effects model	1617	\$\$\$	0.9570 [0.9174: 0.985						350: 0.95901	100.0%
			0.9570 [0.9174, 0.965	58] 100.0%	Random effects model	777		ologoo Tour		
Heterogeneity: $I^{n} = 68\%$, τ^{n} :			٦	58] 100.0%	Heterogeneity: $l^2 = 83\%$, $\tau^2 =$	0.0125, <i>p</i> < 0.0		Clocob Low		
		0.6 0.7 0.8 0.9	1	58] 100.0%	Heterogeneity: $I^2 = 83\%$, $\tau^2 =$	0.0125, <i>p</i> < 0.0	1 0.4 0.5 0.6 0.7 0.8 0.9			
C			1			0.0125, <i>p</i> < 0.0	0.4 0.5 0.6 0.7 0.8 0.9	Proportion		Weight
C	0.5		٦		Heterogeneity: J ² = 83%, τ ² = D Study	0.0125, <i>p</i> < 0.0	0.4 0.5 0.6 0.7 0.8 0.9			
C Study SOF+VEL±RBV	0.5		1 1 Proportion 95%-CI 1	Weight	Heterogeneity: /² = 83%, τ² = D Study SOF+VEL±RBV	0.0125, <i>p</i> < 0.0	0.4 0.5 0.6 0.7 0.8 0.9	Proportion	95%-CI	Weight
C Study SOF+VEL±RBV Alessandra Mangia 2019	0.5 Events Total		1 1 1 1 1 1 1 1 1 1 1 1 1 1	Weight 16.0%	Heterogeneity: /² = 83%, r² = D Study SOF+VEL±RBV Alessandra Mangia 2019	0.0125, <i>p</i> < 0.0	0.4 0.5 0.6 0.7 0.8 0.9	Proportion - 0.9636 [0	95%-CI 8747; 0.9956]	Weight 12.2%
C Study SOF+VEL±RBV Alessandra Mangia 2019 Pamela S. Belperio 2019	0.5 Events Total 147 150 1437 1566		1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1	Weight 16.0% 19.3%	Heterogeneity: /² = 83%, τ² = D Study SOF+VEL±RBV Alessandra Mangia 2019 Parrela S. Belperio 2019	0.0125, <i>p</i> < 0.0 () Events Tota 53 55 136 169	0.4 0.5 0.6 0.7 0.8 0.9	Proportion - 0.9636 [0 0.8047 [0	95%-CI 8747; 0.9956] 7369; 0.8616]	Weight 12.2% 15.9%
C Study SOF+VEL±RBV Alessandra Mangia 2019 Parnela S. Belperio 2019 J. von Felden 2018	0.5 Events Total		1 1 1 1 1 0.9800 [0.9427; 0.9959] 0.9176 [0.9029; 0.3306] 0.9170 [0.3315; 0.3902]	Weight 16.0% 19.3% 16.3%	Heterogeneity: I ² = 83%, τ ² = D Study SOF+VEL±RBV Alessandra Mangia 2019 Pamela S. Belperio 2019 J. von Felden 2018	0.0125, <i>p</i> < 0.0		Proportion - 0.9636 [0 0.8047 [0 0.9273 [0	95%-CI 8747; 0.9956] 7369; 0.8616] 8241; 0.9798]	Weight 12.2% 15.9%
C Study SOF+VEL±RBV Alessandra Mangia 2019 Aramela S. Belperio 2019 J. von Felden 2018 Alessandra Mangia 2019	0.5 Events Total 147 150 1437 1566 162 167		1 1 1 1 1 1 0.9800 [0.9427; 0.9959] 0.9776 [0.9029; 0.9306] 0.9771 [0.9315; 0.9902] 0.9825 [0.9486; 0.9964]	Weight 16.0% 19.3%	Heterogeneity: /² = 83%, τ² = D Study SOF+VEL±RBV Alessandra Mangia 2019 Parrela S. Belperio 2019	0.0125, p < 0.0 (Events Tota 53 55 136 165 51 55		Proportion - 0.9636 [0 0.8047 [0 0.9273 [0 0.9091 [0	95%-CI .8747; 0.9956] .7369; 0.8616]	Weight 12.2% 15.9% 12.2% 9.9%
C Study SOF+VEL±RBV Vessandra Mangia 2019 Parmela S. Belperio 2019 Von Feiden 2018 Vessandra Mangia 2019 Andom effects model Heterogeneity: /² = 89%, ²² =	0.5 Events Total 147 150 1437 1566 162 167 168 171 2054		1 1 1 1 1 1 0.9800 [0.9427; 0.9959] 0.9776 [0.9029; 0.9306] 0.9771 [0.9315; 0.9902] 0.9825 [0.9486; 0.9964]	Weight 16.0% 19.3% 16.3% 16.4%	Heterogeneity: <i>I</i> ² = 83%, x ² = D Study SOF+VE1±RRV Alessandra Mangia 2019 Pamela S. Belperio 2019 J. von Felden 2018 Alessandra Mangia 2019 Random effects model Heterogeneity: <i>I</i> ² = 77%, x ² =	0.0125, p < 0.0 Events Tota 53 55 136 165 51 55 30 33 312		Proportion - 0.9636 [0 0.8047 [0 0.9273 [0 0.9091 [0	95%-Cl 8747; 0.9956] 7369; 0.8616] 8241; 0.9798] 7567; 0.9808]	Weight 12.2% 15.9% 12.2% 9.9%
C Study SOF+VEL&RBV Alessandra Mangia 2019 Pamela S. Belgenori 2019 J. von Folden 2018 Alessandra Mangia 2019 Random effects model Hearogeneity: // e 89%, * ² = GLE+PIB	0.5 Events Total 147 150 1437 1586 162 167 168 171 2054 0.0072, p < 0.01		1 roportion 95%-Cl 1 0.9800 (0.9427; 0.9859) 0.9176 (0.9325; 0.9902) 0.9176 (0.9335; 0.9902) 0.9825 (0.9466; 0.9964) 0.9840 (0.9223; 0.8908)	Weight 16.0% 19.3% 16.3% 16.4% 68.0%	Heterogeneity: $r^2 = 83\%, r^2 =$ D Study SOF+VEL±RBV Alessandra Mangia 2019 Pameia S. Belperio 2019 J. von Felden 2018 Alessandra Mangia 2019 Random effects model Heterogeneity, $r^2 = 77\%, r^2 =$ SOF+VEL+VOX	0.0125, p < 0.0 (Events Tota 53 55 136 166 51 55 30 33 311 0.0123, p < 0.01		Proportion - 0.9636 [0 0.8647 [0 0.9273 [0 0.9091 [0 0.9029 [0	95%-CI 8747; 0.9956] 7369; 0.8616] 8241; 0.9798] 7567; 0.9808] 8128; 0.9674]	Weight 12.2% 15.9% 12.2% 9.9% 50.3%
C Study SOF+VEL±RBV Alessandra Mangia 2019 at von Felden 2018 Ju von Felden 2018 Androm effectes model Heterogenety: /* = 89%, ** = GLE+PIB Akto Nozaki 2020	0.5 Events Total 147 150 1437 1566 162 167 168 171 2054 0.0072, p < 0.01 13 15		I roportion 95%-Cl V 0.9800 [0.9427; 0.9959] 0.9176 [0.9029; 0.3308] 0.9701 [0.3315; 0.9902] 0.9825 [0.9496; 0.9964] 0.9640 [0.9223; 0.9908] 0.8667 [0.5954; 0.9834]	Weight 16.0% 19.3% 16.3% 16.4% 68.0% 6.1%	Heterogeneity: $r^2 = 83\%, r^2 =$ D Study SOF+VEL±RRV Alessandra Mangia 2019 Pamela S. Belperio 2019 J. von Felden 2018 Alessandra Mangia 2019 Random effecta model Heterogeneity: $r^2 = 77\%, r^2 =$ SOF+VEL+VOX Jordi Lianeras 2019	0.0125, p < 0.0 Events Tota 53 55 136 166 51 55 30 33 312 0.0123, p < 0.01 24 36		Proportion - 0.9636 [0 0.8047 [0 0.9273 [0 0.9029 [0 0.9029 [0 0.8000 [0 0.8	95%-CI 8747; 0.9956] 7369; 0.8616] 8241; 0.9798] 7567; 0.9808] 8128; 0.9674] 6143; 0.9229]	Weight 12.2% 15.9% 12.2% 9.9% 50.3%
C Study SOF+VEL&RBV Alessandra Mangia 2019 Pamela S. Belgenori 2019 J. von Foldon 2018 Alessandra Mangia 2019 Random effects model Hearogeneity: /ř = 89%, *² = GLE+PIB Aktio Nozaki 2020 Chi–Yi Chen 2021	0.5 Events Total 147 150 1437 1566 168 171 2054 0.0072, p < 0.01 13 15 71 75		1 reportion 95%-Cl 1 0.9600 [0.9427; 0.9959] 0.9176 [0.3028; 0.3306] 0.95701 [0.315; 0.3902] 0.9525 [0.4486; 0.9964] 0.9640 [0.3223; 0.3966] 0.8667 [0.5954; 0.9834] 0.9467 [0.6680; 0.9853]	Weight 16.0% 19.3% 16.3% 16.4% 68.0% 6.1% 13.5%	Heterogeneity: /² = 83%, *² = D Study SOF+VEL±RBV Alessandra Mangia 2019 Pamela S. Belperio 2019 J. von Felden 2018 Alessandra Mangia 2019 Random efficat model Heterogeneity: /² = 77%, *² = SOF+VEL+VOX Jordi Llaneras 2019 Elisabetto Degasperi 2019	0.0125, p < 0.0 Events Tota 53 55 136 166 51 56 30 33 312 0.0123, p < 0.01 24 30 9 33 42		Proportion - 0.9636 [0 0.8047 [0 0.9273 [0 0.9029 [0 0.8000 [0 0.7857 [0	95%-Cl 8747; 0.9956j 7369; 0.8616j 8241; 0.9798j 7567; 0.9808j 8128; 0.9674j 6143; 0.9229j 6319; 0.8870j	Weight 12.2% 15.9% 12.2% 9.9% 50.3% 9.5% 11.0%
C Study Nessandra Mangia 2019 Amenia S. Belperio 2019 J. von Felden 2018 Mandom effecta model Messandra Mangia 2019 Mandom effecta model Messandra Mangia 2019 Gate-PIB Akto Nozaki 2020 Chi–Yi Ohen 2021	0.5 Events Total 147 150 1437 1566 162 167 168 171 2054 0.0072, p < 0.01 13 15 71 75 57 57		Troportion 95%-Cl V 0.9800 [0.9427; 0.9959] 0.9176 [0.9029; 0.9308] 0.9770 [0.9315; 0.9902] 0.9825 [0.9466; 0.9964] 0.9640 [0.9223; 0.9908] 0.8667 [0.5954; 0.9834] 0.9647 [0.8680; 0.9863] 1.0000 [0.9873; 1.0000]	Weight 16.0% 19.3% 16.3% 68.0% 6.1% 13.5% 12.3%	Heterogeneity: $r^2 = 83\%, r^2 =$ D Study SOF+VEL±RRV Alessandra Mangia 2019 Pamela S. Belperio 2019 J. von Felden 2018 Alessandra Mangia 2019 Random effects model Heterogeneity: $r^2 = 77\%, r^2 =$ SOF+VEL+VOX Jordi Lianeras 2019 Elisabetta Degasperi 2015 Pamela S. Belperio 2019	0.0125, p < 0.0 Events Tota 53 55 136 166 51 56 30 33 311 0.0123, p < 0.01 24 30 33 42 42 45		Proportion - 0.9636 [0 0.8047 [0 0.9091 [0 0.9092] [0 0.80029 [0 0.80029 [0 0.8003 [0 0.7857 [0 0.9333 [0 0.933 [0 0.93	95%-CI 8747; 0.9956] 7369; 0.8616] 8241; 0.9798] 8128; 0.9674] 6143; 0.9229] 6319; 0.8970] 6319; 0.8970]	Weight 12.2% 15.9% 9.9% 50.3% 9.5% 11.0% 11.3%
C Study SOF+VEL&RBV Alessandra Mangia 2019 Pamela S. Belgenoi 2019 J. von Folden 2018 Alessandra Mangia 2019 Random effects model Michael P. Curry 2021 Michael P. Curry 2021 Michael P. Curry 2021 Michael P. Curry 2021	0.5 Events Total 147 150 1437 1566 162 167 168 171 2054 0.0072, p < 0.01 13 15 71 75 57 57 147		1 reportion 95%-C1 1 0.9600 [0.9427; 0.9959] 0.9176 [0.3028; 0.3306] 0.95701 [0.315; 0.3902] 0.9525 [0.4486; 0.9964] 0.9640 [0.3223; 0.3966] 0.8667 [0.5954; 0.9834] 0.9467 [0.6680; 0.9853]	Weight 16.0% 19.3% 16.3% 68.0% 6.1% 13.5% 12.3%	Heterogeneity: /² = 83%, *² = D Study SOF+VEL±RBV Alessandra Mangia 2019 Pamela S. Belperio 2019 J. von Feldera model Heterogeneity: /? = 77%, *? = SOF+VEL+VOX Jordi Llaneras 2019 Elisabetto Degasperi 2019 Pamela S. Belperio 2019 David A. Smith 2021	0.0125, p < 0.0 Events Tota 53 55 136 166 51 55 30 33 312 0.0123, p < 0.01 24 30 9 33 42 42 45 50 66		Proportion - 0.9636 [0 0.8047 [0 0.9029 [0 0.8000 [0 0.8000 [0 0.8000 [0 0.8000 [0 0.8000 [0 0.8086 [0 0.8	95%-Cl 8747; 0.9956] 7369; 0.8616] 8241; 0.9798] 8128; 0.9674] 6143; 0.9229] 6319; 0.8970] 8173; 0.9860] 663; 0.8958]	Weight 12.2% 15.9% 12.2% 50.3% 50.3%
C Study SOF+VEL&RBV Alessandra Mangia 2019 Pamela S. Belgenoi 2019 J. von Folden 2018 Alessandra Mangia 2019 Random effects model Michael P. Curry 2021 Michael P. Curry 2021 Michael P. Curry 2021 Michael P. Curry 2021	0.5 Events Total 147 150 1437 1566 162 167 168 171 2054 0.0072, p < 0.01 13 15 71 75 57 57 147		Troportion 95%-Cl V 0.9800 [0.9427; 0.9959] 0.9176 [0.9029; 0.9308] 0.9770 [0.9315; 0.9902] 0.9825 [0.9466; 0.9964] 0.9640 [0.9223; 0.9908] 0.8667 [0.5954; 0.9834] 0.9647 [0.8680; 0.9863] 1.0000 [0.9873; 1.0000]	Weight 16.0% 19.3% 16.3% 68.0% 6.1% 13.5% 12.3%	Heterogeneity: /² = 83%, *² = D Study SOF+VEL±RRV Alessandra Mangia 2019 Pamela S. Belperio 2019 J. von Felden 2018 Alessandra Mangia 2019 Random effects model Heterogeneity: /² = 77%, *² = SOF+VEL+VOX Jordi Llaneras 2019 Elisabetta Degasperi 2016 Pamela S. Belperio 2019 David A. Smith 2021 Random effects model	0.0125, <i>p</i> < 0.0 Events Tota 53 55 136 166 51 66 51 30 33 312 0.0123, <i>p</i> < 0.01 24 33 42 44 50 66 177		Proportion - 0.9636 [0 0.8047 [0 0.9029 [0 0.8000 [0 0.8000 [0 0.8000 [0 0.8000 [0 0.8000 [0 0.8086 [0 0.8	95%-CI 8747; 0.9956] 7369; 0.8616] 8241; 0.9798] 8128; 0.9674] 6143; 0.9229] 6319; 0.8970] 6319; 0.8970]	Weight 12.2% 15.9% 12.2% 50.3% 50.3%
C Study SOF+VEL&RBV Alessandra Mangia 2019 Pamela S. Belgenori 2019 J. von Foldon 2018 Alessandra Mangia 2019 Random effects model Heterogeneity: /² = 73%, z² = Michael P. Curry 2021 Michael P. Curry 2021 Michael P. Curry 2021	0.5 Events Total 147 150 1437 1566 162 167 168 171 2054 0.0072, p < 0.01 13 15 71 75 57 57 147 0.0154, p = 0.03		1 roportion 95%-C1 V 0.9800 [0.9427; 0.9959] 0.9176 [0.8028; 0.3306] 0.95701 [0.315; 0.9902] 0.9528 [0.9446; 0.9964] 0.9640 [0.8667; 0.5954; 0.96634] 0.9647 [0.5954; 0.9654] 0.9667 [0.5973; 1.0000] 0.96676 [0.8770; 1.0000]	Weight 16.0% 19.3% 16.4% 68.0% 6.1% 13.5% 12.3% 32.0%	Heterogeneity: /² = 83%, *² = D Study SOF+VEL±RBV Alessandra Mangia 2019 Pamela S. Belperio 2019 J. von Feldera model Heterogeneity: /? = 77%, *? = SOF+VEL+VOX Jordi Llaneras 2019 Elisabetto Degasperi 2019 Pamela S. Belperio 2019 David A. Smith 2021	0.0125, <i>p</i> < 0.0 Events Tota 53 55 136 166 51 66 51 30 33 312 0.0123, <i>p</i> < 0.01 24 33 42 44 50 66 177		Proportion - 0.9636 [0 0.8047 [0 0.9029 [0 0.8000 [0 0.8000 [0 0.8000 [0 0.8000 [0 0.8000 [0 0.8086 [0 0.8	95%-Cl 8747; 0.9956] 7369; 0.8616] 8241; 0.9798] 8128; 0.9674] 6143; 0.9229] 6319; 0.8970] 8173; 0.9860] 663; 0.8958]	Weight 12.2% 15.9% 12.2% 50.3% 50.3%
C Study SOF4-VEL&RBV Alessandra Mangia 2019 Arandas E.Belgeric 2019 J. von Foldon 2018 Alessandra Mangia 2019 Random effects model Materogeneity - 2 - 235, c ² = GLEA-IPB Addto Nozaki 2020 Chi–Vi (Den 2021 Michael P. Curry 2021 Random effects model Random effects model	0.5 Events Total 147 150 1427 1566 1427 1566 1427 1566 1427 157 1427 1566 1427 157 1437 156 0.0072, p < 0.01 13 15 71 75 57 57 147 0.0154, p = 0.03 2201		Troportion 95%-Cl V 0.9800 [0.9427; 0.9959] 0.9176 [0.9029; 0.9308] 0.9770 [0.9315; 0.9902] 0.9825 [0.9466; 0.9964] 0.9640 [0.9223; 0.9908] 0.8667 [0.5954; 0.9834] 0.9647 [0.8680; 0.9863] 1.0000 [0.9873; 1.0000]	Weight 16.0% 19.3% 16.4% 68.0% 6.1% 13.5% 12.3% 32.0%	Heterogeneity: <i>I</i> ² = 83%, <i>z</i> ² = D Study SOF+VEL±RRV Alessandra Mangia 2019 Pamela S. Belperio 2019 J. von Felden 2018 Alessandra Mangia 2019 Random effects model Heterogeneity: <i>I</i> ² = 77%, <i>z</i> ² = SOF+VEL+VOX Jordi Llaneras 2019 Elisabetta Degasperi 2016 Pamela S. Belperio 2019 David A. Smith 2021 Random effects model Heterogeneity: <i>I</i> ² = 43%, <i>z</i> ² =	0.0125, <i>p</i> < 0.0 Events Tota 53 55 136 166 51 66 51 30 33 312 0.0123, <i>p</i> < 0.01 24 33 42 44 50 66 177		Proportion - 0.9636 [0 0.8047 [0 0.9029 [0 0.8000 [0 0.8000 [0 0.7857 [0 0.9333 [0 0.8086 [0 0.8086 [0 0.8086 [0 0.8086 [0 0.8086 [0 0.8085 [0 0.8	95%-Cl 8747; 0.9956] 7369; 0.8616] 8241; 0.9798] 8128; 0.9674] 6143; 0.9229] 6319; 0.8970] 8173; 0.9860] 663; 0.8958]	Weight 12.2% 15.9% 12.2% 50.3% 50.3%
C Study SOF4VELSERBV Alessandra Mangia 2019 Pamela S. Belgerio 2019 J. von Foldon 2018 Alessandra Mangia 2019 Random effects model Michael P. Curry 2021 Random effects model Heterogenety: /* = 73%, ** = Random effects model	0.5 Events Total 147 150 1437 1566 162 167 168 171 2054 0.0072, ρ < 0.01 13 15 71 75 57 57 147 0.0154, ρ = 0.03 2201 0.0073, ρ < 0.01		1 roportion 95%-C1 V 0.9800 [0.9427; 0.9959] 0.9176 [0.8028; 0.3306] 0.95701 [0.315; 0.9902] 0.9528 [0.9446; 0.9964] 0.9640 [0.8667; 0.5954; 0.96634] 0.9647 [0.5954; 0.9654] 0.9667 [0.5973; 1.0000] 0.96676 [0.8770; 1.0000]	Weight 16.0% 19.3% 16.4% 68.0% 6.1% 13.5% 12.3% 32.0%	Heterogeneity: /² = 83%, <² = D Study SOF+VEL±RBV Alessandra Mangia 2019 Pamela S. Belperio 2018 Alessandra Mangia 2019 Random defects model Heterogeneity: /² = 77%, <² = SOF+VEL+VOX Jord I Lanera, 2019 Elisabetto Degasperi 2019 Elisabetto Degasperi 2019 Pamela S. Belperio 2019 David A. Smith 2021 Random defects model Heterogeneity: /² = 43%, r² = GLE+PIB	Events Tota 53 55 53 55 51 56 51 56 51 56 51 56 30 33 312 0.0123, p < 0.0 2 33 44 2 43 42 45 45 45 45 45 45 45 45 45 45 45 45 45 4		Proportion - 0.9636 [0 0.8047 [0 0.9273 [0 0.9091 [0 0.9023 [0 0.9033 [0 0.8333 [0 0.83381 [0 0.8381 [0 0	95%-C1 8747: 0.9956j 7369: 0.8616j 8241: 0.9786j 8128: 0.9674j 6143: 0.9229j 6319: 0.9670j 8173: 0.9860j 6863: 0.8950j 7573: 0.9059j	Weight 12.2% 15.9% 12.2% 9.9% 50.3% 11.0% 11.3% 11.3% 12.7% 44.5%
C Study SOF4VELSERBV Alessandra Mangia 2019 Pamela S. Belgerio 2019 J. von Foldon 2018 Alessandra Mangia 2019 Random effects model Michael P. Curry 2021 Random effects model Heterogenety: /* = 73%, ** = Random effects model	0.5 Events Total 147 150 1437 1566 162 167 168 171 2054 0.0072, ρ < 0.01 13 15 71 75 57 57 147 0.0154, ρ = 0.03 2201 0.0073, ρ < 0.01		1 roportion 95%-C1 V 0.9800 [0.9427; 0.9959] 0.9176 [0.8028; 0.3306] 0.95701 [0.315; 0.9902] 0.9528 [0.9446; 0.9964] 0.9640 [0.8667; 0.5954; 0.96634] 0.9647 [0.5954; 0.9654] 0.9667 [0.5973; 1.0000] 0.96676 [0.8770; 1.0000]	Weight 16.0% 19.3% 16.4% 68.0% 6.1% 13.5% 12.3% 32.0%	Heterogeneity: <i>I</i> ² = 83%, <i>x</i> ² = D Study SOF+VEL±RRV Alessandra Mangia 2019 Pamela S. Belperio 2019 J. von Fielden 2018 Alessandra Mangia 2019 Random effects model Heterogeneity: <i>I</i> ² = 77%, <i>x</i> ² = SOF+VEL+VOX Jordi Llaneras 2019 Elisabetta Degasperi 2015 Pamela S. Belperio 2019 David A. Smith 2021 Random effects model Heterogeneity: <i>I</i> ² = 43%, <i>x</i> ² = GLE+PIB Chi-Yi Chen 2021	Events Tota 53 55 136 166 51 56 30 33 42 42 44 50 75 62 50 75 62 51 56 51 56 53 34 31 31 31 31 31 31 31 31 31 31 31 31 31		Proportion - 0.9638 [0] 0.8047 [0] 0.8047 [0] 0.9029 [0] 0.9029 [0] 0.8000 [0] 0.7857 [0] 0.8381 [0] 0.8381 [0] 0.8381 [0] 1.0000 [0]	95%-C1 8747: 0.9956j 7369: 0.8416j 8241: 0.9788j 8128: 0.9674j 6143: 0.9229j 6319: 0.8970j 8173: 0.9860j 6863: 0.8958j 7573: 0.9659j 7573: 0.9659j 7151; 1.0000j	Weight 12.2% 15.9% 12.2% 50.3% 9.5% 11.0% 11.3% 12.7% 44.5%
-	0.5 Events Total 147 150 1437 1566 162 167 168 171 2054 0.0072, ρ < 0.01 13 15 71 75 57 57 147 0.0154, ρ = 0.03 2201 0.0073, ρ < 0.01		1 roportion 95%-C1 V 0.9800 [0.9427; 0.9959] 0.9176 [0.8028; 0.3306] 0.95701 [0.315; 0.9902] 0.9528 [0.9446; 0.9964] 0.9640 [0.8667; 0.5954; 0.96634] 0.9647 [0.5954; 0.9654] 0.9667 [0.5973; 1.0000] 0.96676 [0.8770; 1.0000]	Weight 16.0% 19.3% 16.4% 68.0% 6.1% 13.5% 12.3% 32.0%	Heterogeneity: /² = 83%, <² = D Study SOF+VEL±RBV Alessandra Mangia 2019 Pamela S. Belperio 2018 Alessandra Mangia 2019 Random defects model Heterogeneity: /² = 77%, <² = SOF+VEL+VOX Jord I Lanera, 2019 Elisabetto Degasperi 2019 Elisabetto Degasperi 2019 Pamela S. Belperio 2019 David A. Smith 2021 Random defects model Heterogeneity: /² = 43%, r² = GLE+PIB	Events Tota 53 55 53 55 51 56 51 56 51 56 51 56 30 33 312 0.0123, p < 0.0 2 33 44 2 43 42 45 45 45 45 45 45 45 45 45 45 45 45 45 4		Proportion - 0.9638 [0] 0.8047 [0] 0.8047 [0] 0.9029 [0] 0.9029 [0] 0.8000 [0] 0.7857 [0] 0.8381 [0] 0.8381 [0] 0.8381 [0] 1.0000 [0]	95%-C1 8747: 0.9956j 7369: 0.8616j 8241: 0.9786j 8128: 0.9674j 6143: 0.9229j 6319: 0.9670j 8173: 0.9860j 6863: 0.8950j 7573: 0.9059j	Weight 12.2% 15.9% 12.2% 50.3% 9.5% 11.0% 11.3% 12.7% 44.5%
C Study SOF4-VEL&RBV Alessandra Mangia 2019 Arandas E.Belgeric 2019 J. von Foldon 2018 Alessandra Mangia 2019 Random effects model Materogeneity - 2 - 235, c ² = GLEA-IPB Addto Nozaki 2020 Chi–Vi (Den 2021 Michael P. Curry 2021 Random effects model Random effects model	0.5 Events Total 147 150 1437 1566 162 167 168 171 2054 0.0072, ρ < 0.01 13 15 71 75 57 57 147 0.0154, ρ = 0.03 2201 0.0073, ρ < 0.01		1 roportion 95%-C1 V 0.9800 [0.9427; 0.9959] 0.9176 [0.8028; 0.3306] 0.95701 [0.315; 0.9902] 0.9528 [0.9446; 0.9964] 0.9640 [0.8667; 0.5954; 0.96634] 0.9647 [0.5954; 0.9654] 0.9667 [0.5973; 1.0000] 0.96676 [0.8770; 1.0000]	Weight 16.0% 19.3% 16.4% 68.0% 6.1% 13.5% 12.3% 32.0%	Heterogeneity: /² = 83%, <² = D Study SOF+VEL±RBV Alessandra Mangia 2019 Pamela S. Belperio 2019 J. von Felden 2018 Alessandra Mangia 2019 Random effects model Heterogeneity: /² = 77%, <² = SOF+VEL+VOX Jordi Llareras 2019 Elisabetta Degaperi 2019 Elisabetta Degaperi 2019 Elisabetta Degaperi 2019 Elisabetta Degaperi 2019 Elisabetta Degaperi 2019 Elisabetta Degaperi 2019 Chi-Yi Chen 2021 Random effects model Heterogeneity: /² = 43%, <² =	Events Tota 53 55 136 166 51 56 30 33 42 42 44 50 75 62 50 75 62 51 56 51 56 53 34 31 31 31 31 31 31 31 31 31 31 31 31 31		Proportion - 0.9636 [0 0.8047 [0 0.8047 [0 0.9023 [0 0.9023 [0 0.9023 [0 0.9023 [0 0.9033 [0 0.9056 [0 0.8035 [0 0.8035 [0 0.9033 [0 0.9056 [0 0.8335 [1 0 0.9335 [1 0 0.9335 [1 0 0.9335 [1 0 0.9335 [1 1.0000 [0 1.0000 [0 1.0000 [0 1.0000 [0 1.0000 [0 1.0000 [0 [1 1.0000 [0 [1	95%-C1 8747: 0.9956j 7369: 0.8416j 8241: 0.9788j 8128: 0.9674j 6143: 0.9229j 6319: 0.8970j 8173: 0.9860j 6863: 0.8958j 7573: 0.9659j 7573: 0.9659j 7151; 1.0000j	Weight 12.2% 15.9% 12.2% 50.3% 9.9% 50.3% 9.5% 11.0% 11.3% 44.5% 5.2%

FIGURE 4

The forest plots of the 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.

CI: 82.89-96.90%) in cases that received SOF+VEL \pm RBV, 94.44% (95% CI: 77.68-100%) in cases that received GLE+PIB, and 82.84% (95% CI: 57.06-98.90%) in cases that received SOF+VEL+VOX.

Stratification assessment of treatmentnaive cases

The subgroup assessment of the treatment-naive cases showed that the pooled SVR12/24 rate in cases that received GLE+PIB and SOF+VEL \pm RBV was 96.79% (95% CI: 93.37-99.13%), as presented in Figure 4C. In addition, the SVR rate in cases that received GLE +PIB and SOF+VEL \pm RBV was 96.76% (95% CI: 87.10-100%) and 96.40% (95% CI: 92.23-99.08%), respectively.

Stratification assessment of treatmentexperienced cases

The pooled SVR12/24 rate for the treatment-experienced cases with HCV-GT3 infection that received SOF+VEL+VOX, SOF+VEL \pm RBV, and GLE+PIB was 88.41% (95% CI: 82.67-93.22%), as presented in Figure 4D. Furthermore, the corresponding SVR12/24 rate was 83.81% (95% CI: 75.73-90.59%), 90.29% (95% CI: 81.28-96.74%), and 100% (95% CI: 84.93-100%), respectively.

Risk of bias and quality assessment

Detailed data on all genotypes instead of genotype 3 HCV patients in the majority of included articles were available, as shown in Table 1. The risk of bias due to missing data was moderate or high, as presented in Figure 5. The Egger's test showed no significant publication bias (t=0.51, DF=17, P=0.6150).

Discussion

With the approval of the direct-acting antivirals, the landscape of HCV treatment has significantly changed since 2015. New regimens and their combinations have been researched to resolve difficulties through antiviral therapy.

The pooled SVR12 rate of 3,177 HCV-GT3 patients who received SOF+VEL \pm RBV, GLE+PIB, and SOF+VEL+VOX was 94.00% in the meta-analysis of rates in real-world settings. Patients with decompensated cirrhosis, prior DAA treatment-failure, HBV/ HCV or HCV/HIV coinfection, chronic kidney disease, HCC, or a prior liver transplant who were considered difficult to treat were involved. The SVR12 rate was 90.50% (n=694/777) and 95.70% (n=1508/1617) in the patients with and without cirrhosis, respectively, and 88.41% (n=430/502) and 96.79% (n=2055/2201) in the treatment-experienced and treatment-naïve patients, respectively. A decrease of approximately 5.20% in the SVR rate in the patients with cirrhosis and an 8.38% decrease in the treatment-experienced patients were observed. Thus, the fibrosis

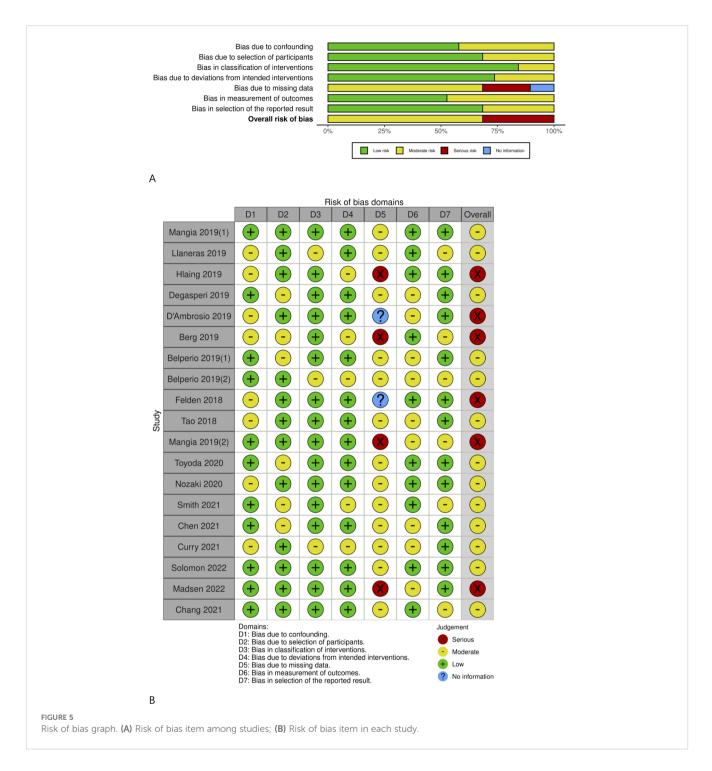
stage and history of antiviral treatment might significantly impact the antiviral effectiveness. Furthermore, the fibrosis stage and particularly treatment history may significantly affect the SVR rates.

In the ASTRAL-3 study reported by Foster et al. (37), the SVR12 rate was 97% (n=191/197) and 91% (n=73/80) in HCV GT3 patients without cirrhosis and with compensated cirrhosis, respectively, and 97% (n=200/206) and 90% (n=64/71) in treatment-naïve and treatment-experienced patients, respectively. A retrospective study on patients who had compensated cirrhosis or advanced fibrosis had an SVR12 rate of 95% (n=145/153) in GT3 patients (38). Through subgroup analysis, the SVR12 rate of the treatment-experienced patients prescribed SOF+VEL ± RBV was 90.29% (n=270/312), which was lower than that of the treatmentnaive patients (96.40%, n=1914/2054). Similar decreases were observed in the subgroup populations that received SOF+VEL +VOX. The SVR12 rate of patients with cirrhosis treated with SOF+VEL \pm RBV was 91.10% (n=647/723), which was lower than that of patients without cirrhosis (94.61%, n=1339/1439), as well as that those that received GLE+PIB and SOF+VEL+VOX.

High SVR rates of patients with GLE+PIB have been reported in registration trials in recent years, ranging between 95% and 100% (39). The effect of HCV genotype, fibrosis stage, history of antiviral treatment, HCC, and advanced chronic kidney disease (CKD) on the efficacy of GLE+PIB seemed to be limited because of the excellent SVR rate (30). In the present analysis, the SVR12 rate of GT3 patients treated with GLE+PIB was 96.96% (n=429/448) in real-world settings. When analyzing a subgroup of patients with cirrhosis and treatment experience, the SVR rate results did not fluctuate significantly, mirroring those reported in previous trials.

Belperio et al. reported that among 13 GT3 patients with prior SOF/VEL exposure, the SVR rates were 100% (n=6/6) in those without cirrhosis and 71.4% (n=5/7) in those with cirrhosis. Thus, they considered that cirrhosis occurring with prior SOF/VEL exposure may augment the risk of relapse rather than cirrhosis alone (25). All the GT3 patients enrolled in the four studies of this meta-analysis that received SOF+VEL+VOX were treatment-experienced with SOF/LDV, OBV/PTV-r+DSV, SOF/VEL, or SOF/DCV. The pooled SVR12 rate was 83.81% (n=149/179) in the patients with and without cirrhosis. The SVR rate of the patients with cirrhosis and prior DAA exposure was 82.84% (n=30/36) and 92.68% (n=36/39), respectively, compared to the patients with prior DAA exposure but without cirrhosis and prior DAA failure were a more difficult-to-treat cohort.

Previous studies indicated that genotype 3 HCV with variants such as A30K, L31M, and Y93H of NS5A was refractory (40–42). Zeuzem et al. (40) reported that in the ENDURANCE-3 trial, GT3 patients with the A30K mutation at baseline had a lower SVR12 rate. However, most patients achieved SVR regardless of the A30K variant. In the ASTRAL-3 study, an SVR rate of 84% in patients with Y93H substitution compared to that of 97% in patients without the substitution was attained from patients who received SOF/VEL (37). Sarrazin et al. (43) reported that SVR12 rates were similar in patients with/without NS3 and/or NS5A resistance-associated variants (RASs) and patients with/without VOX- or VEL-specific



RASs who received SOF + VEL + VOX for 12 weeks. Seven articles in this meta-analysis (19, 21, 22, 25, 26, 30, 31) completed the RAVs test, concluding that RASs may not be associated with a lower SVR rate. Nozaki et al. (30) indicated that the effect of RASs on therapeutic results was limited because of the 99.1% overall SVR12 rate. It may not be necessary to test for RASs before treatment because of the high SVR rates in patients completing therapy.

The limitations of this meta-analysis included high heterogeneity in the baseline characteristics and clinical features of the patients, along with a small number of patients who received SOF+VEL+VOX. More studies are needed in order to analyze the real-world antiviral effectiveness of DAAs in chronic HCV GT3-infected patients.

Conclusions

In conclusion, SOF+VEL \pm RBV, GLE+PIB, and SOF+VEL +VOX had good antiviral effectiveness for chronic HCV-GT3 infection in real-world settings. Factors such as cirrhosis and treatment experience, especially previous DAA treatment failure, may influence the SVR rate.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

LZ: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. JL: Methodology, Writing – review & editing. YZ: Methodology, Writing – original draft. SJ: Data curation, Investigation, Writing – review & editing. HX: Funding acquisition, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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