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**Hepatitis C virus genotype 3: Meta-analysis on sustained virologic response rates with currently available treatment options**

Ampuero J *et al.* Treatment of HCV genotype 3

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**Abstract**

**AIM:** To address the therapeutic efficacy of various treatment regimens in genotype 3 selecting randomized clinical trials and prospective National Cohort Studies.

**METHODS:**  (1) PEG-INF-based therapy including sofosbuvir (SOF) + RBV for 12 wk *vs* SOF+RBV 24w; (2) SOF+RBV therapy 12 w/16w *vs* 24w; and (3) the role of RBV in SOF + daclatasvir (DCV) and SOF + ledipasvir (LDV) combinations. This meta-analysis provides robust information with the intention of addressing treatment strategy for hepatitis C virus genotype 3.

**RESULTS:** A combination treatment including SOF+RBV+PEG-IFN for 12 wk notes better SVR than with only SOF + RBV for 12 wk, although its association with more frequent adverse effects may be a limiting factor. Longer duration therapy with SOF + RBV (24 wk) has achieved higher SVR rates than shorter durations (12 or 16 wk). SOF+LDV are not an ideal treatment for genotype 3.

**CONCLUSION:** Lastly, SOF+DCV combination is probably the best oral therapy option and the addition of RBV does not appear to be needed to increase SVR rates substantially.

**Key words:** Hepatitis C; Genotype 3; Sofosbuvir; Daclatasvir; Ledipasvir

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**Core tip:** The landscape of therapy for hepatitis C virus infection is changing rapidly. In genotype 3, the improvement in SVR rates has not been hugely spectacular, being considered the most difficult genotype to treat and representing a major challenge. The advent of direct acting antivirals has not solved all questions about the treatment, while challenges remain such as the use of RBV, the duration of PEG-IFN-free treatment and whether PEG-IFN still plays an important role. These questions are difficult to elucidate with the current data because of the small number of patients included in clinical trials (particularly, those with cirrhosis) and their different designs.

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**INTRODUCTION**

The landscape of therapy for hepatitis C virus (HCV) infection is changing rapidly[1]. Ideally, new drugs should be all-oral regimen (once-daily, single pill) with pangenotypic activity, and have short treatment course (no more than 12 wk), and with high sustained virological response (at least 90%-95%). A multitude of direct acting antivirals (DAAs) have been developed with or without pegylated interferon (PEG-IFN) and ribavirin (RBV)[2], and others are being tested in promising clinical trials[3]. In genotype 3, the improvement in SVR rates has not relatively suboptimal and is being considered the most difficult genotype to treat and thus representing a major challenge[4]. Unique clinical features of genotype 3 and possible reasons for suboptimal response are: (1) a close relationship with insulin resistance and disturbances in lipid metabolism[5]; and (2) fibrosis progression[6] and higher incidence of hepatocellular carcinoma[7].

The advent of DAAs has not solved all questions regarding the treatment in genotype 3, and with emerging new challenges such as RBV use[8], duration of PEG-IFN-free treatment and whether PEG-IFN still plays an important role[9]. These questions are difficult to elucidate with the current data because of the small number of patients included in clinical trials (particularly, those with cirrhosis) and their different designs. In fact, more valuable data have been derived from prospective observational studies (clinical practice), and beyond randomized clinical trials. In this study, we aimed to address key questions on treatment outcomes through a meta-analysis.

**MATERIAL AND METHODS**

***Data sources and search***

The search strategy was in accordance with the recommendations of meta-analysis of clinical trials and observational studies. We searched in MEDLINE, EMBASE and Cochrane Library databases (to November 2015), as well as abstracts published and presented at EASL and AASLD (to November 2015) to identify potentially relevant publications in English language. We included FDA-approved DAA therapies that included SVR as a primary end point. Search terms were: “hepatitis C”, “genotype 3”, “HCV treatment”, “sofosbuvir”, “ledipasvir”, “daclatasvir”, “ribavirin”, “interferon”. The preceding terms were combined with appropriate Boolean logic. Manual search of cited bibliographies was also performed. Duplicated publications were deleted. Two researchers independently performed the literature search and data abstraction with regard to the inclusion and exclusion criteria by reading titles and abstracts. When reading titles and abstracts did not allow identification of eligible studies, articles were read in full. Relevant reviews and letters to the editor were excluded from the analysis, but read in full to identify potential relevant original studies. Disagreements between two observers were resolved by discussion.

***Study selection criteria and data extraction***

We selected randomized clinical trials (preferably) and prospective National Cohort Studies in which therapies were administrated in different arms. Therefore, studies including only a combination testing different doses or being administrated to different subset of patients were excluded. Inclusion and exclusion criteria (studies involving genotypes other than 3) were defined prior to initiation of the literature search. Twelve studies were included and classified according to the aims (Figure 1). The following data were extracted: (1) Study: year of publication, number of patients, location, design; (2) Patients: stage of liver disease (cirrhosis or chronic hepatitis), previous HCV treatment (naïve or treatment-experienced); (3) HCV treatment regimen and duration; and (4) SVR rates.

***Objectives***

We aimed to address the therapeutic efficacy of various treatment regimens in genotype 3. Firstly, we compared a PEG-INF-based therapy including sofosbuvir (SOF) + RBV during 12 wk with SOF + RBV 24 w. Secondly, we assessed the importance of extending the course of SOF+RBV therapy (12 w/16 w *vs* 24w). Thirdly, we analyzed the role of RBV in SOF + daclatasvir (DCV) and SOF + ledipasvir (LDV) combinations.

***Statistical analysis***

Statistical analysis was performed using the Meta-Disc software 1.4[10], considering: (1) a summary of data from individual studies; (2) an investigation of the studies homogeneity, graphically and statistically; (3) calculation of clustered indexes; and (4) exploration of heterogeneity. Our assumption of heterogeneity was tested for each planned analysis using the Cochran-*Q* heterogeneity and I2 statistics (low, moderate, and high heterogeneity according to I2 values of 25%, 50%, and 75%, respectively)[11]. Random effects model using Der Simonian and Laird method and fixed effects model were used according to the presence of heterogeneity. To check for publication bias, we used the Begg and Egger tests. Only two-sided tests with a significance level of 0.05 were used. Confidence intervals (CIs) of individual studies were determined or approximated from the available data. Further, we assessed the quality of the studies using the ‘‘Quality Assessment of Diagnostic Accuracy Studies” (QUADAS) tool for observational studies (≥ 10 were considered as high-quality studies[12]) and Jadad scale for randomized clinical trials (≥ 3 were considered as high-quality ones[13]).

**RESULTS**

***Comparison between INF-based and IFN-free regimens***

We evaluated four studies that met the selection criteria and that were identified using the search strategy described. Studies characteristics are shown inTable 1. Pooled data included 807 patients. The meta-analysis demonstrated that triple therapy including SOF+RBV+PEG-IFN was able to achieve higher SVR rates (92.5%; 236/255) than SOF+RBV (75.2%; 415/552), using fixed effects model [OR = 3.51 (95%CI: 2.08–5.92)] (Figure 2A). We found neither heterogeneity between these studies [(Cochran-*Q* = 0.94; df = 3, *P* = 0.8157); inconsistency *I*2 = 0%, and τ2 = 0.0000)] nor publication bias [(Begg test: Kendall’s tau 1.70, *P* = 0.1); (Egger test: -1.14, *P* = 0.37)].

***Course of SOF+RBV treatment***

We included four studies involving 850 patients. The meta-analysis demonstrated that a 24w-course of SOF+RBV (85.5%; 501/586) combination was better than 12w-16w (70%; 185/264) in terms of SVR rates, using random effects model [OR = 3.51 (95%CI: 1.59–7.70)] (Figure 2B). We found a moderate heterogeneity between these studies [(Cochran-Q = 7.77, df = 3, *P* = 0.0511); inconsistency *I*2 = 61%, and τ2 = 0.3718], but no publication bias [(Begg test: Kendall’s tau 0.34, *P* = 0.73); (Egger test: 0.81, *P* = 0.50)]. Three of these studies evaluated SVR rates according to the presence of cirrhosis. In non-cirrhotic patients, longer therapy of SOF+RBV (89.7%; 218/243) achieved higher SVR rates than shorter one (78.2%; 144/184) using random effects model (OR 2.44 (95%CI: 1.41–4.23)). We did find a moderate heterogeneity between these studies [(Cochran-*Q* = 4.42; df = 2, *P* = 0.11); inconsistency *I*2 = 55%, and τ2 = 0.3987], with no publication bias. Similarly, this effect was observed in cirrhotic population (78.5%; 73/93 *vs* 55%; 38/69) using the random effects model [OR = 2.79 (95%CI: 1.34–5.78)].

***Role of RBV in SOF+DCV and SOF+LDV combinations***

Additionally, we assessed the role of adding RBV in IFN-free regimens. Four studies have evaluated this point regarding the combination treatment of SOF+DCV. Pooled data included 502 patients. The meta-analysis demonstrated that adding RBV was not essential to achieve optimal SVR rates (83%; 173/209 *vs* 86.3%; 253/293), using fixed effects model [OR = 1.09 (95%CI: 0.35–3.40)] (Figure 2C). We did not find heterogeneity between these studies [(Cochran-*Q* = 2.38; df = 3, *P* = 0.4981); inconsistency *I*2 = 0%, and τ2 = 0.0000], and did not seem to have publication bias. On the other hand, two studies have evaluated the role of adding RBV in SOF+LDV combination. Pooled data included 169 patients. The meta-analysis demonstrated that adding RBV was important to achieve better SVR rates (81%; 111/137 *vs* 62.5%; 20/32), using fixed effects model [OR = 3.30 (95%CI: 1.35–8.04)] (Figure 2D). We did not find heterogeneity between these studies [(Cochran-*Q* = 0.61, df = 1, *P* = 0.4335); inconsistency *I*2 = 0%, and τ2 = 0.0000], and no publication bias was found [(Begg test: Kendall’s tau 0.01, *P* = 0.99)].

**DISCUSSION**

New challenges have emerged in the evolving era of HCV therapy, particularly with genotype 3, and these include the ongoing role of PEG-IFN, the addition of RBV and the adequate duration of the therapy[13]. The rapid development and use of DAAs in several heterogeneous studies including small number of patients has made robust guideline development and recommendation rather challenging. Thus, a meta-analysis is needed pooling all patients to address these questions.

In this new era, PEG-IFN is being abandoned as part of standard HCV therapy because of the association with serious adverse effects (and the parenteral administration) [14]. From now on, PEG-IFN will not be used for genotypes 1, 2 or 4 anymore. For genotype 3, there are only two DAAs (SOF and DCV) with a significant inhibitory activity *in vitro*[15]. In this context, PEG-IFN could potentially play a role in HCV treatment and could be the last such indication for its use. We demonstrated that the addition of PEG-IFN to SOF+RBV 12w was superior to only SOF+RBV combination (92% *vs* 75%; OR = 3.51). BOSON study represents the main study evaluating this comparison, and it included nearly two hundred patients per arm[16]. Additionally, DCV has been evaluated in combination with PEG-IFN+RBV, although SVR rates were not higher than those patients treated with dual standard therapy (65% *vs* 59%)[17]. Both EASL and AASLD recommend SOF+RBV+PEG-IFN as a good alternative in non-cirrhotic and compensated-cirrhotic patients[18]. On the other hand, no data is available evaluating SOF+RBV+PEG-IFN *vs* SOF+DCV.

We analyzed the combination of SOF+RBV, in terms of duration of therapy. To date, this combination has been evaluated for 12, 16 and 24 wk duration. We compared SOF+RBV 12w/16w *vs* SOF+RBV 24w, and the latter achieved higher SVR rates (89% *vs* 70%, OR = 3.51). Furthermore, SOF+RBV 12w (56%) was associated with poorer SVR rates than dual standard therapy with PEG-IFN+RBV 24w (63%) in FISSION study[19], and showing similar results than POSITRON study (61%)[20]. Both studies demonstrated that SOF+RBV combination 12w was suboptimal, especially in the cirrhotic population. In FISSION study, a longer course of therapy (16w) with SOF + RBV showed better results than a shorter one (62% *vs* 30%)[21]. Overall SVR rates with SOF + RBV 12/16w were about 60%, which is considered suboptimal in the evolving era of hepatitis C therapy where response rates far below 90% are considered suboptimal. We included four studies that evaluated the course of 24 wk of SOf+RBV and noted an overall SVR rate around 90%. In addition, PHOTON study confirmed the extrapolation of these results in HIV-coinfected patients[22]. Taking into account all of these results, EASL and AASLD guidelines recommend extending SOF+RBV treatment to 24 wk (especially indicated in non-cirrhotic population).

In this meta-analysis, we demonstrated that SOF+LDV combination needs the addition of RBV to achieve optimal SVR rates in patients with genotype 3 (81% *vs* 62%, OR = 3.30). In contrast, RBV did not play any role in the combination of SOF+DCV because it did not improve SVR rates. DCV and LDV are HCV NS5A inhibitors[23], although DCV shows a pangenotypic activity[24] while LDV has a low activity in genotypes 2 and 3[25]. Currently, SOF+DCV combination is the first option to treat patients with genotype 3 in EASL guidelines, 12 wk in non-cirrhotic and 24 weeks (with RBV) in cirrhotic patients. This recommendation is mainly based on ALLY-3 study in which SOF+DCV 12w achieved 97% and only 58% SVR in non-cirrhotic and cirrhotic population respectively[26]. The UK Early Access Program did not show any impact of adding RBV to SOF+DCV 24w in cirrhotic patients (70% *vs* 71%)[27], as well as the European Compassionate Use Program in patients at high risk of hepatic decompensation or death within 12 mo (100% *vs* 85%; *P* = NS) [28]. In a relatively small study, ELECTRON-2 trial, SOF+LDV for 12w achieved suboptimal SVR rates while the addition of RBV substantially increased it (100% in non-cirrhotic naïve patients, and 89% in non-cirrhotic and 73% in cirrhotic treatment-experienced patients)[29]. However, this trial should be interpreted with caution because it has very limited data from a phase II single-center study and comprising a homogenous population which could limit the generalizability of the results. This, together with the high EC50 of LDV for genotype 3[30], has lead EASL and AASLD to not recommend SOF+LDV±RBV combination for genotype 3.

Recommendations made by EASL and AASLD guidelines were based on few data derived from randomized clinical trials and, due to the rapid and wide use in clinical practice, modified by prospective national cohorts. This meta-analysis provides solid and robust information to address several important questions, regarding the treatment of HCV genotype 3. First, combination including SOF+RBV+PEG-IFN shows better results than only SOF+RBV, although its association with adverse effects may limit the use (*i.e.,* cirrhotic population). Second, longer therapies including SOF+RBV (24 wk) have higher SVR rates than shorter ones (12 or 16 wk). Therefore, SOF+RBV for 24 wk are ideal. Third, SOF+LDV should not be used in genotype 3 and, if so, necessarily with RBV. Lastly, SOF+DCV combination is probably the best option and the addition of RBV does not appear to be needed to increase substantially the SVR rates.

**COMMENTS**

***Background***

The advent of direct acting antivirals (DAAs) has not solved all questions of successfully and effectively treating all hepatitis C virus (HCV) genotypes. Genotype 3, a common genotype globally, remains the last challenge. It remains unclear if Peg-IFN and RBV are still required to treat HCV genotype 3 effectively.

***Research frontiers***

The current data are inadequate to strongly take a position on the duration of therapy with DAAs, the role of ribavirin and PEG-IFN particularly given the heterogeneity of the HCV population that includes prior treatment experience with or without cirrhosis, and the small number of patients in the various clinical trials.

***Innovations and breakthroughs***

The authors demonstrated that SOF+LDV combination needs the addition of RBV to achieve optimal SVR rates in patients with genotype 3 (81% *vs* 62%, OR = 3.30).

***Peer-review***

The meta-analysis HCV genotype 3: Meta-analysis with available treatment options is an important topic and of high scientific significance. The results were interesting and valuable to communicate. This study will help future work in the treatment of HCV. statistical analysis reported in this manuscript are well done.

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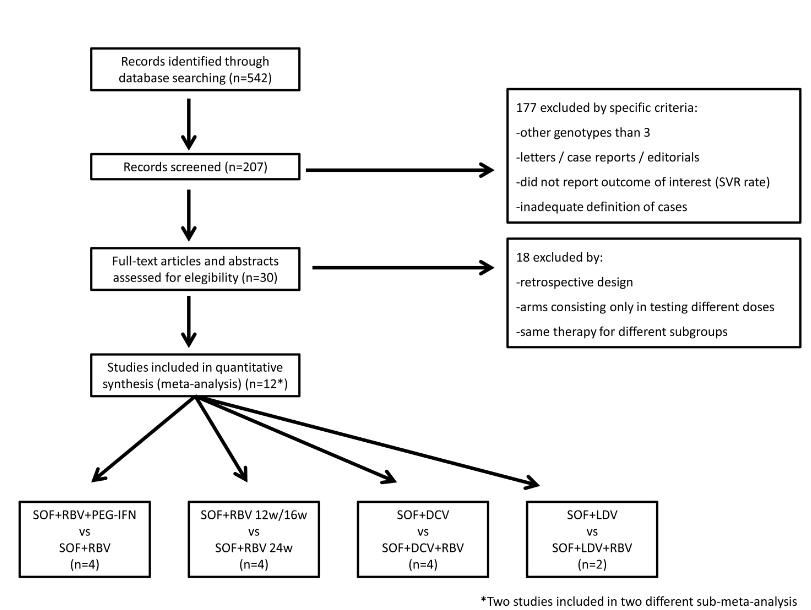
36 **Sulkowski MS**, Gardiner DF, Rodriguez-Torres M, Reddy KR, Hassanein T, Jacobson I, Lawitz E, Lok AS, Hinestrosa F, Thuluvath PJ, Schwartz H, Nelson DR, Everson GT, Eley T, Wind-Rotolo M, Huang SP, Gao M, Hernandez D, McPhee F, Sherman D, Hindes R, Symonds W, Pasquinelli C, Grasela DM. Daclatasvir plus sofosbuvir for previously treated or untreated chronic HCV infection. *N Engl J Med* 2014; **370**: 211-221 [PMID: 24428467 DOI: 10.1056/NEJMoa1306218]

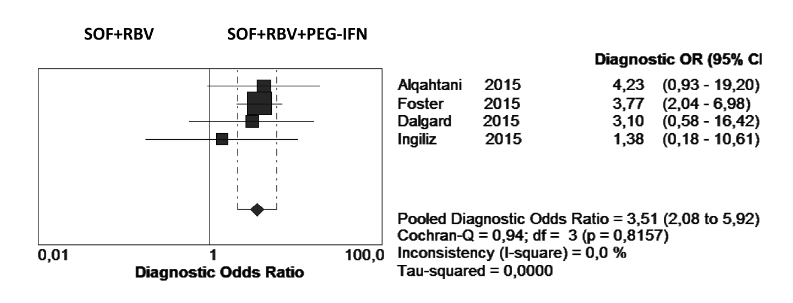
37 **Zeuzem S**, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, Illeperuma A, Svarovskaia E, Brainard DM, Symonds WT, Subramanian GM, McHutchison JG, Weiland O, Reesink HW, Ferenci P, Hézode C, Esteban R. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014; **370**: 1993-2001 [PMID: 24795201 DOI: 10.1056/NEJMoa1316145]

**P-Reviewer:** Abd El-Wahab EW **S-Editor:** Qi Y **L-Editor: E-Editor:**

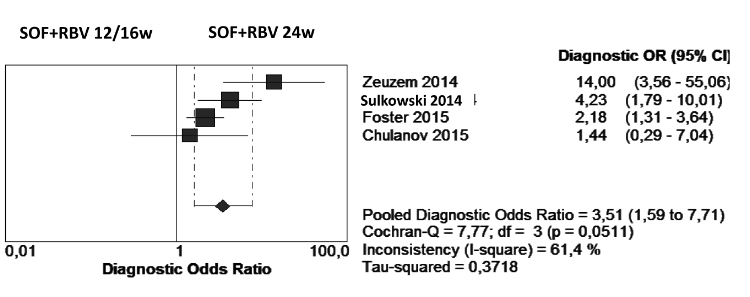
**Table 1 Overall characteristics of studies included in meta-analysis**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Patients characteristics** | **Study design** | **Outcome (SVR %)** |
| Alqahtani *et al*[31] | 2015 | -HCV mono-infected patients.  -TARGET cohort.  -Randomized by cirrhosis and previous treatment.  -50% Treatment naïve.  -51% Cirrhosis. | a) SOF + RBV + PEG-IFN (*n* = 18)  b) SOF + RBV (*n* = 133) | a) 89%  b) 65% |
| Chulanov *et al*[32] | 2014 | -HCV mono-infected patients.  -Russian multicenter cohort.  -Randomized by cirrhosis.  -100% Treatment naïve.  -18% Cirrhosis. | a) SOF + RBV 16 w (*n* = 30)  b) SOF + RBV 24 w (*n* = 31) | a) 87%  b) 90% |
| Dalgard *et al*[33] | 2015 | -HCV mono-infected patients.  -Scandinavian cohort study.  -51% Treatment naïve.  -82% Cirrhosis. | a) SOF + RBV + PEG-IFN 12 w (*n* = 25)  b) SOF + RBV 24 w (*n* = 33) | a) 92%  b) 79% |
| Foster *et al*[17]  (BOSON) | 2015 | -HCV mono-infected patients.  -Randomized study.  -51% Treatment naïve.  -31% Cirrhosis. | a) SOF + RBV + PEG-IFN 12 w (*n* = 181)  b) SOF + RBV 16 w (*n* = 181)  c) SOF + RBV 24 w (*n* = 182) | a) 93%  b) 71%  c) 84% |
| Foster *et al*[27] | 2015 | -HCV mono-infected patients.  -NHS England Early Access Program.  -100% Decompensated Cirrhosis. | a) SOF + DCV 12 w (*n* = 7)  b) SOF + DCV + RBV 12 w (*n* = 113)  c) SOF + LDV 12 w (*n* = 7)  d) SOF + LDV + RBV 12 w (*n* = 61) | a) 71%  b) 81%  c) 57%  d) 72% |
| Gane *et al*[29] (ELECTRON-2) | 2015 | -HCV mono-infected patients.  -Randomized study.  -50% Treatment naïve.  -32% Cirrhosis. | a) SOF + LDV 12 w (*n* = 25)  b) SOF + LDV + RBV 12 w (*n* = 26)  c) SOF + LDV + RBV 12 w (*n* = 50) | a) 64%  b) 100%  c) 82% |
| Hezode *et al*[34] | 2015 | -HCV mono-infected patients.  -French Compassionate Use Program.  -27% Treatment naïve.  -94% Cirrhosis. | a) SOF + DCV 12 w (*n* = 26)  b) SOF + DCV + RBV 12 w (*n* = 4)  c) SOF + DCV 24 w (*n* = 35)  d) SOF + DCV + RBV 24 w (*n* = 13) | a) 85%  b) 100%  c) 91%  d) 92% |
| Ingiliz *et al*[35] | 2015 | -HCV-HIV co-infected patients.  -German multicenter cohort study  -50% Treatment naïve.  -38% Cirrhosis. | a) SOF + RBV + PEG-IFN 12 w (*n* = 31)  b) SOF + RBV 24 w (*n* = 23) | a) 94%  b) 91% |
| Sulkowski *et al*[22]  (PHOTON) | 2014 | -HCV-HIV co-infected patients.  -International multicenter cohort.  -25% Treatment naïve. | a) SOF + RBV 12 w (*n* = 42)  b) SOF + RBV 24 w (*n* = 123) | a) 67%  b) 89% |
| Sulkowski *et al*[36] | 2014 | -HCV mono-infected patients.  -Randomized study.  -100% Treatment naïve.  -14% Cirrhosis. | a) SOF + DCV 24 w (*n* = 13)  b) SOF + DCV + RBV 24 w (*n* = 5) | a) 92%  b) 80% |
| Welzel *et al*[28] | 2015 | -HCV mono-infected patients.  -European Compassionate Use Program.  -72% Cirrhosis. | a) SOF + DCV 24 w (*n* = 11)  b) SOF + DCV + RBV 24 w (*n* = 13) | a) 100%  b) 85% |
| Zeuzem *et al*[37] (VALENCE) | 2014 | -HCV mono-infected patients.  -Randomized study.  -41% Treatment naïve.  -24% Cirrhosis. | a) SOF + RBV 12 w (*n* = 11)  b) SOF + RBV 24 w *n* = 250) | a) 27%  b) 84% |

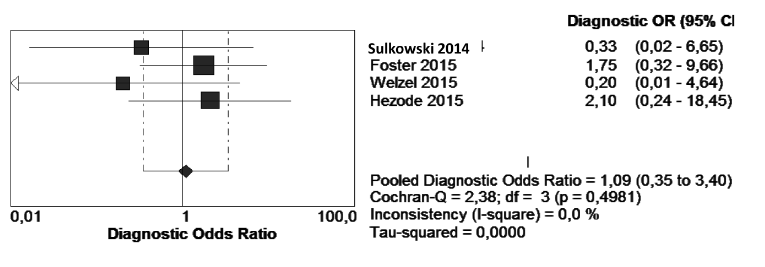
 **Figure 1 Flow chart of studies screened and included in meta-analysis.**



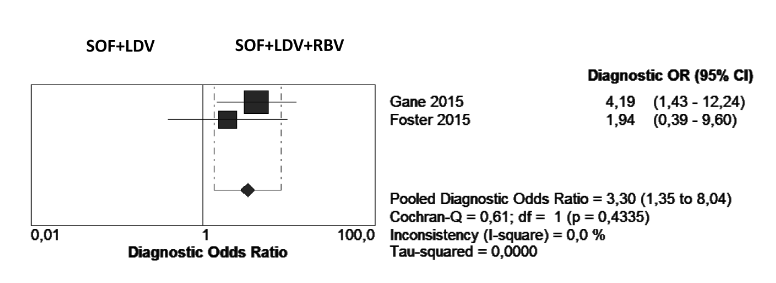
**A**



**B**



**C**



**D**

**Figure 2 Odds ratio (95%CI) and Forest plot for SVR rates.**  A: SOF+RBV+PEG-IFN *vs* SOF+RBV combinations; B: SOF+RBV 12w/16w *vs* SOF+RBV 24w combinations; C: SOF+RBV 12w/16w *vs* SOF+RBV 24w combinations; D: SOF+LDV *vs.* SOF+LDV+RBV combinations.