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Short title: Extra-hepatic manifestations after HCV cure

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Abbreviations

HCV, hepatitis C virus

SVR, sustained virological response

OR, Odds Ratio

CI, confidence interval

SMD, standardized mean differences

GRADE, Grading of Recommendations Assessment, Development and Evaluation

FACIT-FS, Functional Assessment of Chronic Illness Therapy – Fatigue Scale

FSS, Fatigue Severity Scale

KEYWORDS: hepatitis C; extrahepatic manifestations; meta-analysis; antiviral therapy.

ABSTRACT

Background & Aims: Extrahepatic manifestations of hepatitis C virus (HCV) are responsible for morbidity and mortality in many chronically infected patients. New, interferon-free antiviral treatment regimens, that present the opportunity to treat all HCV patients, call for a better understanding of the benefits of treating non-cirrhotic chronically infected individuals.

Methods: A systematic review was conducted. Identified studies from targeted database searches on Embase and Medline were screened. The methodological quality of the included publications was evaluated. Random-effect model meta-analyses were performed. Strength of evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation system.

Results: Data were extracted from a total of 48 identified studies. Achieving sustained virological response (SVR) was associated with reduced extrahepatic mortality (versus no SVR, Odds Ratio (OR) 0.44, 95%CI [0.28; 0.67]). SVR was associated with higher complete remissions in patients with cryoglobulinemia vasculitis (OR 20.76 [6.73; 64.05]), and a higher objective response in those with malignant B-cell lymphoproliferative diseases (OR 6.49 [2.02; 20.85]). Achieving SVR was also associated with reduced insulin resistance at follow-up (OR 0.42 [0.33; 0.53]), and a significant protective effect on the incidence of diabetes (OR 0.34 [0.21; 0.56]). Lack of randomized data comparing SVR versus non-SVR patients for the relevant extrahepatic indications attenuated these analyses.

Conclusion: Antiviral therapy can reduce extrahepatic manifestations related to HCV when SVR is achieved. Higher quality data, and reporting over longer follow-up periods, will be required to thoroughly explore comprehensive HCV treatment strategies.

SHORT SUMMARY 'BOX':

- **What is already known about this subject?**
  - Chronic HCV all-cause mortality was found to be double that of HCV-negative individuals. While liver cirrhosis and hepatocellular carcinoma account for many of HCV related deaths, extrahepatic manifestations have been demonstrated to play a role in HCV mortality rates.
- **What are the new findings?**
  - In patients with chronic HCV infection, achieving sustained virological response (SVR) versus no SVR was associated with reduced extrahepatic mortality.
  - SVR was associated with higher complete remissions in patients with cryoglobulinemia vasculitis, and a higher objective response in those with malignant B-cell lymphoproliferative diseases.
  - Achieving SVR was also associated with a good impact on glucose metabolism, i.e. reduced insulin resistance at follow-up, and a significant protective effect on the incidence of diabetes.
- **How might it impact on clinical practice in the foreseeable future?**
  - Extrahepatic manifestations in HCV infected patients are independent of the severity of the liver disease. Antiviral therapy can reduce not only hepatic manifestations of HCV but also many extrahepatic manifestations related to HCV when SVR is achieved.

INTRODUCTION

Hepatitis C virus (HCV) is a widespread blood borne pathogen estimated to have infected more than 70 million individuals [1]. First isolated in 1989 [2], HCV is responsible for both hepatic and extrahepatic manifestations. Chronic infection has been estimated to develop in 70% of cases [3], with two-thirds of patients presenting extrahepatic manifestations [4]. Overall, chronic HCV all-cause mortality was found to be double that of HCV-negative individuals [5]. And while liver cirrhosis and hepatocellular carcinoma account for many of 700 000 annual HCV related deaths [1], extrahepatic manifestations have been demonstrated to play a role in HCV mortality rates [6-9].

Autoimmune and lymphoproliferative disorders were among the first extrahepatic manifestations associated with hepatitis C virus infection to have been reported, ranging from cryoglobulinemia vasculitis to malignant B-cell lymphoma [10]. Large cohort studies have since revealed additional extrahepatic manifestations, including cardiovascular, neurologic, metabolic and renal conditions [5-9, 11, 12]. And multiple manifestations often coexist in the same patient. Altogether these findings highlight the public health burden of extrahepatic manifestations associated with hepatitis C virus infection. Treatment of HCV patients therefore demands complex multidisciplinary management [13]. Alternatively, a curative panoptic approach of viral eradication has been reported to reduce extrahepatic mortality [11, 12, 14, 15]. Antiviral therapy has since become more attractive with the advent of direct-acting antiviral agents; the reduced duration of such orally administered regimens have been shown to result in greater than 90% cure rates [1]. The need for effective viral eradication measures is thus suggested. The aim of this study is to assess the impact of achieving sustained virological response (SVR) to antiviral treatments on the extrahepatic morbidity and mortality in patients with chronic hepatitis C.

Herein the results of a systematic review and meta-analysis are presented, providing an overview of the currently available evidence for an alleviation of extrahepatic manifestations upon achieving SVR.

METHODS

A systematic review of the literature was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines [16]. Eligibility criteria for use in subsequent meta-analysis were developed, as outlined in the **Appendix 1**. Briefly, publications describing treatment interventions that assessed the effects of SVR versus a comparator group of non-SVR or untreated patients on extrahepatic mortality or morbidity were retained. Two investigators independently performed all of the screening of abstracts, data extraction, risk of bias and GRADE scoring described below. Any selection discrepancies were resolved by a third investigator.

Search Strategy

A comprehensive search of the literature for relevant English language publications from 1989 until a data lock point of 19 June 2017 was conducted using the databases Embase and Medline, as detailed in the **Appendix 2.** Two sets of search queries sought those publications with the word “extrahepatic” were in the title, abstract, or keywords, and in parallel individual searches were conducted using the appropriate MeSH or EMTREE terms for each commonly reported extrahepatic manifestation: overall extrahepatic mortality, cryoglobulinemia vasculitis, B-cell lymphoproliferative diseases, arthralgia/myalgia, sicca syndrome, cardiovascular diseases, renal insufficiency, insulin resistance, diabetes mellitus, fatigue, depression, and cognitive impairment.

Study Selection

All of those abstracts identified in the literature search were scanned, those of potential interest were selected for full text review. Additional articles were obtained through manual inspection of the most recent relevant meta-analyses found through in the Cochrane library, and among the any articles identified. Only those studies with more than 10 patients that compared effects in SVR versus non-SVR patients compared to baseline in a two-arm analysis were selected. Effects on extrahepatic mortality, as well as any reduction of the extrahepatic manifestations listed above were retained.

Data Extraction

Data were extracted on study characteristics, interventions, patient characteristics at baseline, and outcomes for the study populations.

Risk of Bias

The ROBINS-I tool was adapted and used to evaluate the risk of bias in non-randomized studies [15]. Biases considered were reporting, confounding, attrition, and disease-progression, and each category was scored as high risk, low risk, unclear risk, or not applicable.

Meta-analysis and Statistics

SAS 9.4 software (SAS Institute, Cary, NC) was used for this meta-analysis. The analysis was conducted as 12 distinct meta-analyses to assess the 12 topics described above. A random effects model was used to study the correlation of SVR and the reduction of extrahepatic morbidity and mortality for binary data, while continuous numerical scores were compared using standard mean differences.

In the meta-analyses of dichotomous outcomes, we calculated the Odds Ratios (ORs) with 95% confidence intervals (CIs) using 2 × 2 tables from the original articles to evaluate the efficacy of anti-viral treatment between the SVR and no SVR groups whenever possible, or the treatment and control groups. Pooled-effect sizes with 95% CIs were calculated using a random effects model using the Der Simonian and Laird method based on the inverse-variance approach.

In the meta-analyses of continuous outcomes, we used the mean value and standard deviation (SD) or changes from baseline and SD. When SDs were not provided, we performed within-study imputations to handle missing information from published studies. The available means and SD from all the studies with complete information were used to calculate the coefficient of variation (Bracken 1992). The standardized mean differences (SMD) were calculated using the inverse-variance random-effects method.

Heterogeneity was determined using the I^2 test which measures the percentage of total variation across studies. I^2 was calculated as follows: I^2 (%) = 100 × (Q-df)/Q, where Q is Cochrane's heterogeneity statistic and df signifies the degree of freedom. Negative values for I^2 were set to zero, and an $I^2 \geq 75\%$ was considered to be of substantial heterogeneity. Significance was set at p = 0.05.

Quality and Strength of Evidence

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which classifies data as high, moderate, low and very low quality evidence, was used to assess the strength of evidence where comparative estimates of meta-analyses have been provided. No studies of randomized data comparing SVR versus non-SVR patients for the relevant extrahepatic indications were identified in the literature. As such, "high quality evidence" could not be assigned to any of the ensuing meta-analyses. Scoring results were thus limited to moderate, low and very low quality, with +1, 0, or -1 being attributed for risk of bias, consistency of results (as scored by heterogeneity I^2), precision (i.e. p-value, OR), publication bias, and magnitude of effect.

Risk of bias comparisons, as described in the previous section, were pooled to include all of the studies providing data for each meta-analysis. Consistency rose in those analyses wherein the heterogeneity of combined of direct evidence was limited (i.e. an $I^2 < 75\%$). Because no "true" direct comparisons were identified in the literature and indirect evidence contributed to comparisons, indirectness rate was assigned neutral score of 0 for all studies. The level of precision was scored using the p-value, for example, a score of +1 was assigned to those meta-analyses where the 95% CI around the OR was statistically significant ($P<0.001$) for a comparison. Publication bias was rated depending on the symmetrical or asymmetrical distribution of the studies as presented in the funnel plot. Finally, the magnitude of effect was positively rated when absolute effect difference was ≥10%.

RESULTS

Embase and Medline searches for evidence of the effects of SVR on HCV extrahepatic manifestations yielded a total of 2270 articles after the removal of duplicates. Screening these abstracts eliminated 1886 articles as case studies or general review articles, or due to lack of relevant data. A further 57 articles were identified through upon manual screening of meta-analyses and other articles identified through the Cochrane database. Altogether a total of 498 publications were obtained and reviewed in further detail. Of these, 48 studies contained extrahepatic outcome data that allowed for subsequent meta-analysis (**Figure 1)**. For three of the extrahepatic indications investigated, sicca syndrome, myalgia, and cognitive impairment, no publications that would permit further analyses were identified. For all of the retained articles, patient baseline characteristics from these studies are summarized in **Appendix 3**.

For each indication analyzed, data source risk of bias scores (**Appendix 4**), together with the significance and magnitude of the observed effect were part of the GRADE scoring of the quality and strength of evidence (**Appendix 5**). Of note, all data included herein required the extraction of selected patient subpopulations of SVR versus non-SVR, and was thus considered non-randomized.

Impact of SVR on extrahepatic mortality

Four studies reported on extrahepatic mortality: three included all-comers HCV patients (references), while one was restricted to HCV patients with vasculitis [16]. A random effects model performed including all four studies showed that SVR achievement was correlated with a significant reduction in extrahepatic mortality: OR 0.44 [95%CI 0.28; 0.67, p>0.001] (**Figure 2**). Moreover, little heterogeneity between the populations was observed (I^2=0.0%), and the strength of evidence was scored as moderate. Similar results were obtained when excluding the study restricted to patients presenting with vasculitis (**Appendix 6**).

Impact of SVR on cryoglobulinemia vasculitis

A total of sixteen selected studies reported on SVR and cryoglobulinemia vasculitis. Complete remission was reported in eleven studies while at least one observed improvement (including clinical,

immunological or radiological) was reported in all sixteen studies. A significant effect of SVR achievement on complete remission was observed: OR 20.76 [95%CI 6.73; 64.05, p=0.01] (**Figure 3**). The meta-analysis on any observed improvement showed similar results: OR 27.24 [95%CI 10.99;67.53, p=0.001] in favor of the SVR group (**Appendix 7**). A degree of asymmetry was observed in the funnel plots of these data; the strength of evidence is "Low" (**Appendix 4**).

Impact of SVR on lymphoproliferative diseases

Partial and complete responses were reported in five identified publications of the effect of achieving SVR on lymphoproliferative diseases. Random effect model showed a significant effect of SVR achievement on objective responses: OR 6.49 [95%CI 2.02; 20.85, p=0.0017] (**Figure 4**).

Impact of SVR on insulin resistance

The effect of SVR on insulin resistance was studied in eleven of the identified studies. Data from four studies revealed a significant effect of SVR achievement on the frequency of insulin resistance in patients without diabetes: OR 0.42 [95%CI 0.33; 0.53, p<0.001] (**Figure 5a**). The data was found to be homogeneous (I^2=0.0%), and no publication bias was observed. According to GRADE, the strength of evidence is "Moderate" (**Appendix 4**).

The mean homeostasis model assessment of insulin resistance (HOMA-IR) score at follow-up was reported in ten of the studies assessing insulin resistance in all HCV patients (diabetes status at baseline not stated) (n=5 studies) or in HCV patients without diabetes at baseline (n=5 studies). Standardized mean difference was of 0.66 point [95%CI 0.38; 0.94, p<0.001], between SVR and non-SVR groups in the global meta-analysis; meaning that SVR achievement significantly reduced the mean HOMA-IR, by approximately 0.66 (**Figure 5b**). There was, however, a relatively high level of heterogeneity (I^2=74.9%), with an asymmetry observed in the funnel plot of these data; the strength of evidence is "Low" (**Appendix 4**).

In a separate analysis, first excluding studies of HCV patients without diabetes at baseline, similar results were observed: SMD= 0.94 point [95%CI 0.61; 1.26, p<0.001]. The strength of evidence was scored as low by GRADE. Likewise, in patients without diabetes at baseline, meta-analysis showed

also a significant effect with a SMD of 0.48 point [95%CI 0.05; 0.92, p=0.0283]. The strength of evidence is “Very Low” according to GRADE (**Appendix 4**).

Impact of SVR on diabetes

Meta-analysis of data from seven studies showed that SVR achievement has a significant protective effect on diabetes frequency at follow-up: OR 0.34 [95%CI 0.21; 0.56] (**Figure 6**). The strength of evidence is “Moderate” according to GRADE. In three of these studies that did not report diabetes status at baseline, a separate meta-analysis failed to show a significant effect of SVR. However, meta-analysis of four studies of HCV patients clearly designated as being without diabetes at baseline revealed a significant protective effect of SVR achievement on the incidence of *de novo* diabetes: OR 0.27 [95%CI 0.18; 0.40] (**Appendix 8**). The strength of evidence is “Moderate” according to GRADE (**Appendix 4**).

Impact of SVR on arthralgia

Two studies were identified that compared arthralgia in SVR versus non-SVR. Random effect model performed including both studies showed a slight trend, however non-statistically significant, of SVR achievement reducing the incidence of arthralgia: OR 0.86 [95%CI 0.49; 1.52] (**Appendix 9**).

Impact of SVR on cardiovascular risk

Two studies were identified that compared the incidence of cardiovascular events in SVR versus non-SVR. Data from these two studies could not, however, be pooled together, because of the differences in the comparison groups (SVR versus non-SVR [17], and interferon-based treatment versus no treatment [18]). In the study of Nahon et al. [17], a significant effect of SVR achievement on the incidence of major adverse cardiovascular events was reported (OR 0.37 [95%CI 0.59; 0.84]) (**Appendix 10A**). Data from Hsu et al. [18] were used to perform a second random effect model that demonstrates a reduction in the incidence of ischemic events in patients treated for HCV infection: OR 0.70 [95%CI 0.07; 0.31] (**Appendix 10B**).

Impact of SVR on renal impairment risk

Although three publications were identified that assessed the effect of HCV treatment on the reduction of renal events (including end stage renal disease, dialysis, and chronic kidney disease) [12], all appear to have analyzed data from a single population. Retaining the largest data set here to demonstrate the observed effects [18] revealed the effect of treatment (primarily interferon based) on reducing renal events: OR 0.15 [95%CI 0.07; 0.31] (**Appendix 11**).

Impact of SVR on fatigue and depression

Eight publications analyzing the impact of SVR achievement on fatigue were identified; they presented data from a total of ten different studies. As a variety of different tools are used to measure fatigue, separate analyses were performed where comparisons were feasible.

A random effect model performed on results from two studies shows the effect of SVR achievement in reducing the presence of fatigue at follow-up: OR 0.52 [95%CI 0.29; 0.93] (**Appendix 12A**).

A second analysis was performed comparing the results of the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-FS) at follow-up, pooled from two publications describing three different studies (**Appendix 13A**). The FACIT-FS score is ranging from 0 to 52. A score of less than 30 indicates severe fatigue. The higher the score, the better is the quality of life. Data from these different studies was not particularly homogeneous (I^2 = 66.7%), and no significant difference between SVR versus non-SVR patients was observed, as shown by the Standardized Mean Difference (SMD) = 0.07 [-0.29; 0.43], p = 0.6936.

Finally, an analysis using the change from baseline of Fatigue Severity Scale (FSS) scores was performed. The FSS score is ranging from 0 to 7. The higher the score, the higher is the fatigue. A score of more than 5.5 indicates severe fatigue. A significant difference was found when comparing the FSS change from baseline of SVR versus non-SVR patients using data from five different studies: SMD = 0.30 [0.06; 0.54, p = 0.0130] (**Appendix 13B**), although heterogeneity was significantly high (I^2 = 86.6%) (**Appendix 5**).

According to GRADE score attributed, the strength of evidence is “very low” for all three of these analyses.

Although two studies were identified that permitted a direct comparison of depression between SVR versus non-SVR in the HCV populations, no significant reduction in the presence of depression was observed after SVR achievement: OR 0.59 [95%CI 0.11; 3.07] (**Appendix 12B**). According to GRADE score attributed, the strength of evidence is “very low”.

DISCUSSION

Although progressive hepatic fibrosis is responsible for most HCV morbidity and mortality [19], studies with a 5 to 12-year follow-up have suggested that non-cirrhotic patients in particular benefit from a significant decrease in mortality upon achieving SVR [20]. In this meta-analysis data was extracted from 48 predominantly prospective and retrospective cohort studies that examined the effect of achieving SVR on a variety of extrahepatic outcomes in HCV patients. The combined data from four of these HCV study populations, including more than 7000 patients, confirmed that achieving SVR reduced extrahepatic mortality (OR 2.29, [95%CI 1.49;3.52]; p<0.001). In addition, publications addressing twelve recognized extrahepatic indications were sought. Patients achieving SVR were found more likely to have an improvement in cryoglobulinemia vasculitis (OR 27.24, [95%CI 10.99;67.53]; p=0.01). SVR was found to have improved objective responses in five publications studying malignant lymphoproliferative diseases (OR 6.49, [95%CI 2.02; 20.85]; p=0.0017). Among patients without diabetes, those achieving SVR were less likely to harbor insulin resistance (OR 0.42, [95%CI 0.33; 0.53]; p<0.001), and SVR tended to protect patients from developing diabetes (OR 0.27 [95%CI 0.18; 0.40]).

Lymphoproliferative disorders, which range from cryoglobulinemia vasculitis to B-cell lymphomas, used to play to play a major role in HCV extrahepatic mortality; these indications were the most frequently represented in this meta-analysis. Cryoglobulinemia vasculitis is potentially fatal, with a reported 10-year mortality rate of up to 40% [21], and a risk of developing non-Hodgkin B-cell lymphoma 30 times greater than that of the general population [22]. A higher incidence of B-cell non-Hodgkin lymphoma has been linked to HCV in a meta-analysis of seven studies that included over 10,000 patients [23], as well as by large retrospective studies in the US population [24]. In cases with concomitant HCV infection, certain B-cell lymphomas have been reported to have distinct characteristics [25, 26], as well as higher mortality rates [24]. Antiviral treatment is part of the recommended first-line therapies in such cases [13, 27]. Of note, the statistical point of view of the present metaanalysis may have blurred that the reversibility of some malignant lymphoproliferative diseases may depend on histological subtype.

Metabolic disorders have also been closely linked to HCV infection [28]. Herein the effect of SVR on insulin related metabolic diseases represented the second largest group of studies found. The prevalence of insulin resistance or type 2 diabetes mellitus is elevated among HCV-infected patients compared with the general population [28-30]. The development of these conditions may exacerbate the progression of hepatic lesion during HCV infection [31, 32]. According to some [33, 34], although not all [35], international guidelines antiviral treatment should be promptly initiated in HCV patients with insulin resistance or diabetes, along with standard care for these diseases [13, 36]. Frequently prescribed medications for diabetes such as sulfonylureas and insulin have been suggested to increase the risk of hepatocellular carcinoma in HCV patients [37], thus the control of type 2 diabetes should be achieved with other means in patients with underlying advanced liver disease

Analyses of the effect of successful HCV antiviral treatments on other extrahepatic indications were hindered for a variety of different reasons. Despite the identification of ten different studies comparing the impact of SVR on fatigue, the use of different scoring assays impeded the analysis of much of this data. Likewise, although depression has been reported to occur in 25% of HCV infected patients [29], the two study populations pooled herein were unable to provide conclusive evidence for the reduction depression upon achieving SVR. In the case of studies exploring renal impairment risks, a single population appears to have been analyzed in all three of the publications identified. Limited data noted the positive effect of SVR on arthralgia and cardiovascular risks, but only limited statistical analysis was feasible, and no studies that addressed the sicca syndrome, porphyria cutanea tarda, myalgia or cognitive dysfunction were identified.

More broadly, those analyses that were feasible bear a number of limitations. Subpopulations of larger studies were extracted to permit comparisons, as such, none of the data used for meta-analyses could be considered as originating from randomized populations. In addition, the very high SVR rate (>90%) obtained with new interferon-free direct-acting antiviral regimens (reviewed in [38]) has had unfortunate repercussions for meta-analyses. These remarkable success rates, along with the relatively short follow-up required for achieving SVR and limited reporting on other clinical outcomes, have been discussed [39]. In many such studies, after the extraction of extrahepatic subgroups no internal

non-SVR controls remained [40, 41], thus prohibiting data extraction for statistical analysis in this study. In future clinical trials longer term follow-up of patients, and more extensive reporting of a variety of clinical outcomes, will be vital to promote a more thorough understanding of the risk-benefit profiles of these treatments. Finally, interferon alpha may have additional positive effects compared to DAA on some extrahepatic manifestations such as lymphoproliferative diseases. Conversely, DAA are probably better for depression or insulin resistance.

Since the development of direct acting, non-interferon, antiviral regimens, the main international guidelines support the treatment of all patients HCV infected patients, with the exception of those with a short life-expectancy (reviewed in [13]). Although these recommendations do not account for economic criteria, Younossi et al. estimated that direct medical costs for the extrahepatic manifestation of HCV, in the USA alone, to be $1506 million (range $922 to 2208 million) [29]. Similarly, extensive savings to be derived from offering antiviral treatment to all HCV patients have been projected in European health care settings [42, 43]. Given adequate testing to identify chronically infected individuals, these potential savings reflect the compelling opportunity that such safe and highly effective treatments offer to diminish the health care burden caused by HCV morbidity and mortality [44, 45].

In conclusion, extrahepatic manifestations in HCV infected patients are either rare but very severe on the short term (i.e. cryoglobulinemia vasculitis, lymphoproliferative diseases), or very frequent with a potential severity on the mid-long term (i.e. insulin-resistance, type 2 diabetes, cardiovascular diseases, renal impairment…). In most cases, they are independent of the severity of the liver disease. Antiviral therapy can reduce not only hepatic manifestations of HCV but also many extrahepatic manifestations related to HCV when SVR is achieved.

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FIGURE LEGENDS

Figure 1: PRISMA Flow diagram for identification of relevant studies.

Figure 2: Impact of SVR on extrahepatic mortality: Meta-analysis of extrahepatic mortality

Figure 3: Impact of SVR on cryoglobulinemia vasculitis: Meta-analysis of complete remission in patients with cryoglobulinemia vasculitis

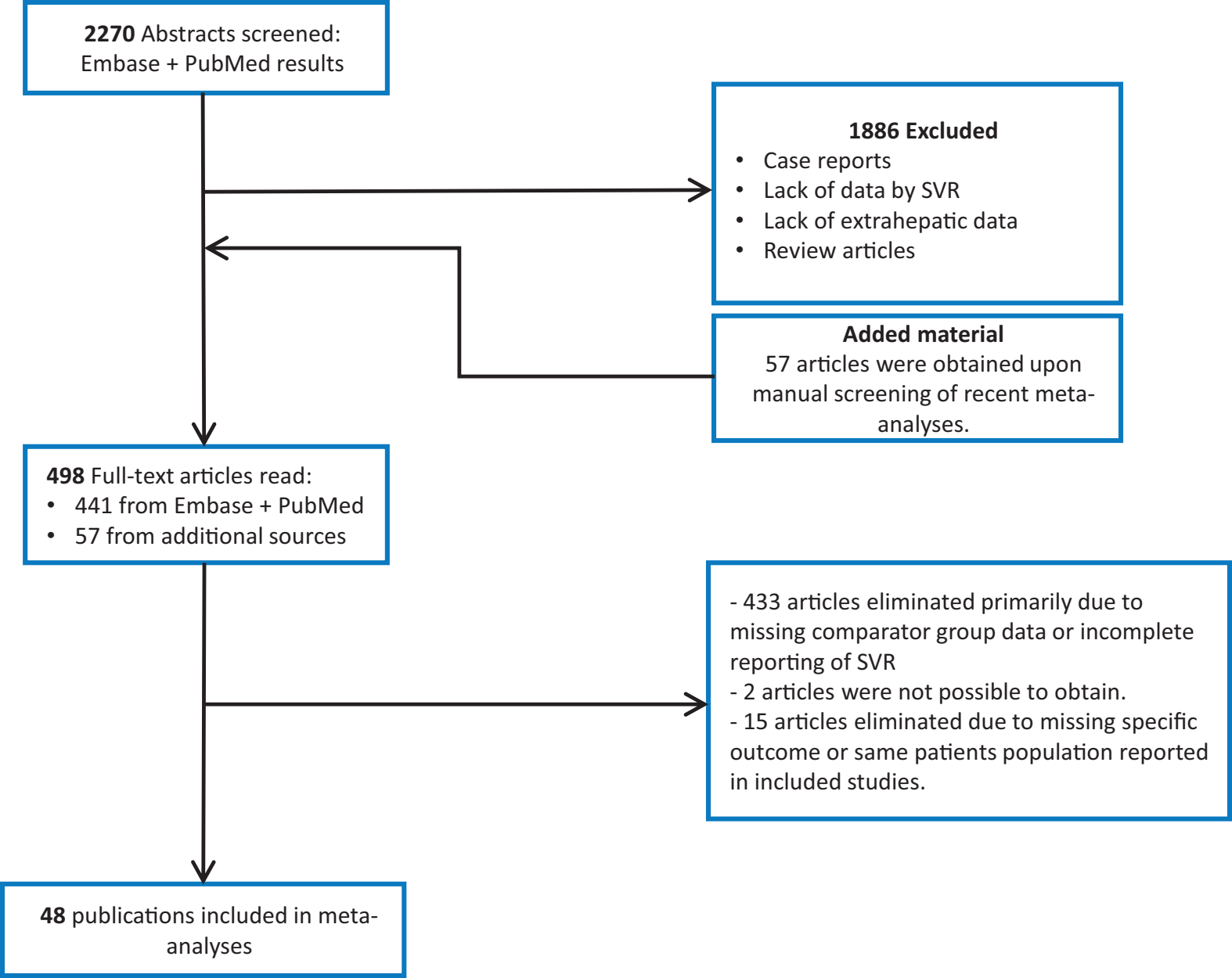
Figure 4: Impact of SVR on lymphoproliferative diseases: Meta-analysis of objective responses in patients with malignant lymphoproliferative diseases

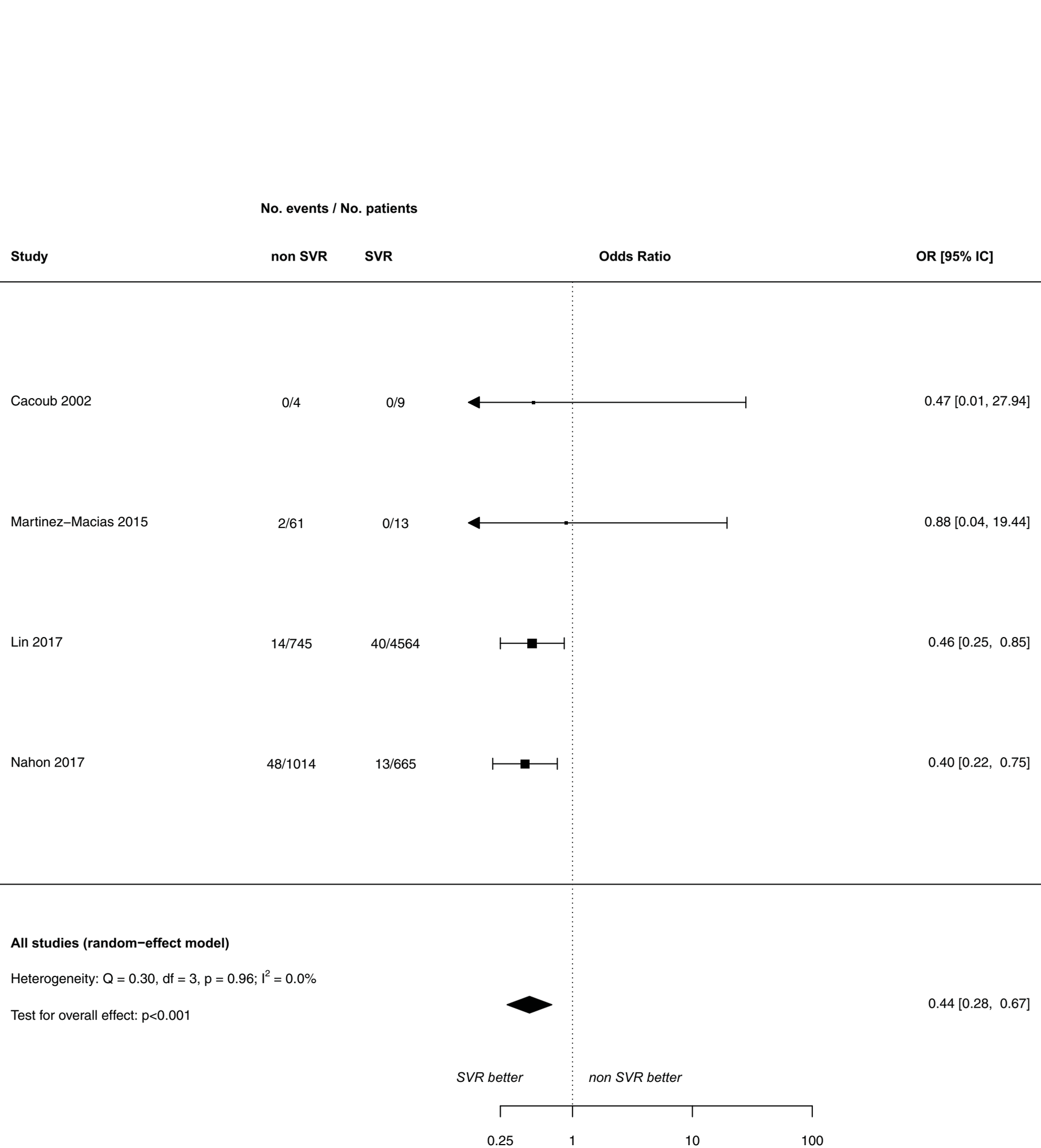
Figure 5: Impact of SVR on insulin resistance

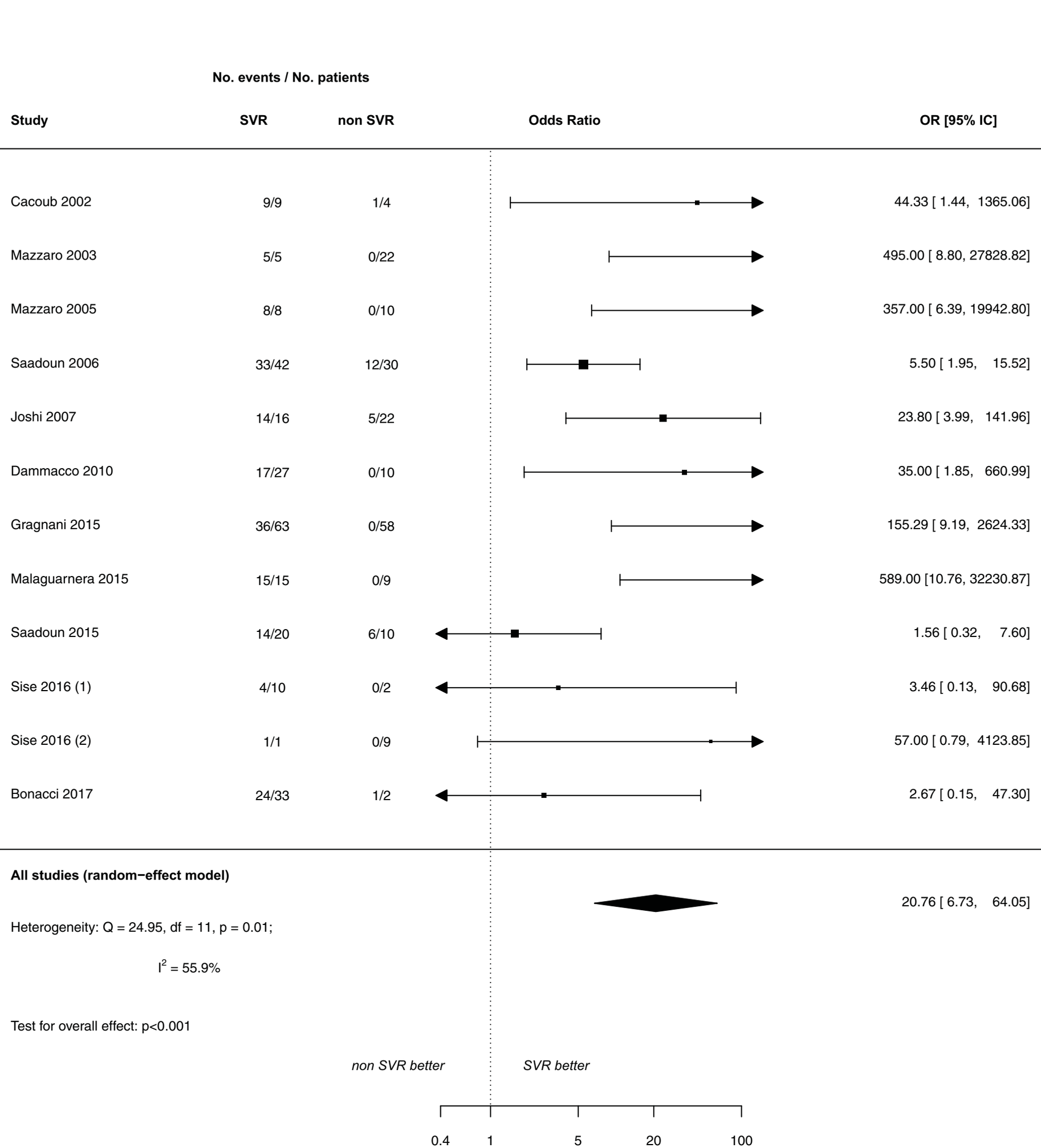
(a) Meta-analysis of insulin resistance at follow-up in HCV patients without diabetes at baseline (4 studies)

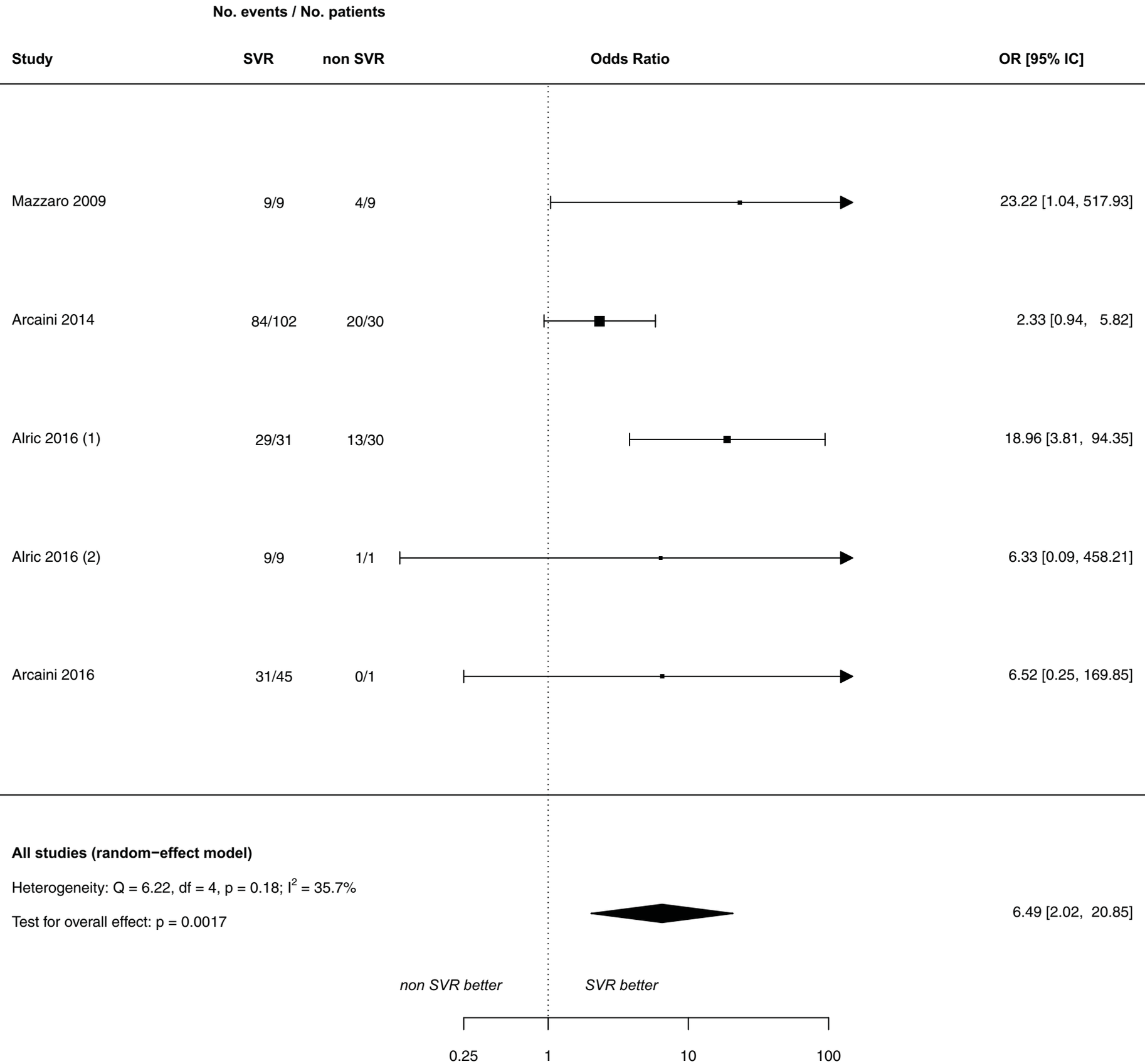
(b) Meta-analysis of mean HOMA-IR in HCV patients with or without diabetes (10 studies)

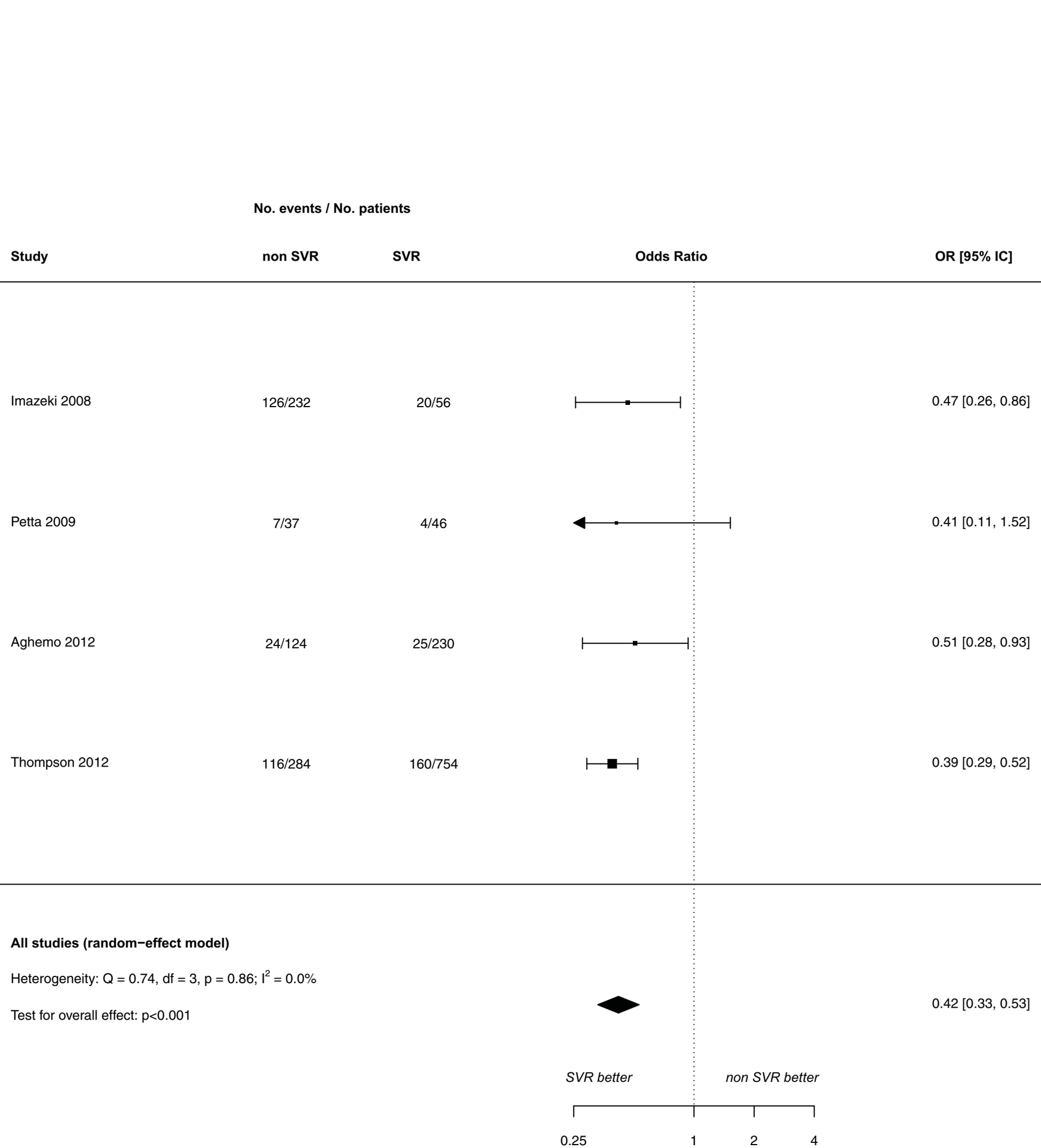
Figure 6: Impact of SVR on diabetes: Meta-analysis of presence of diabetes after SVR achievement in HCV patients

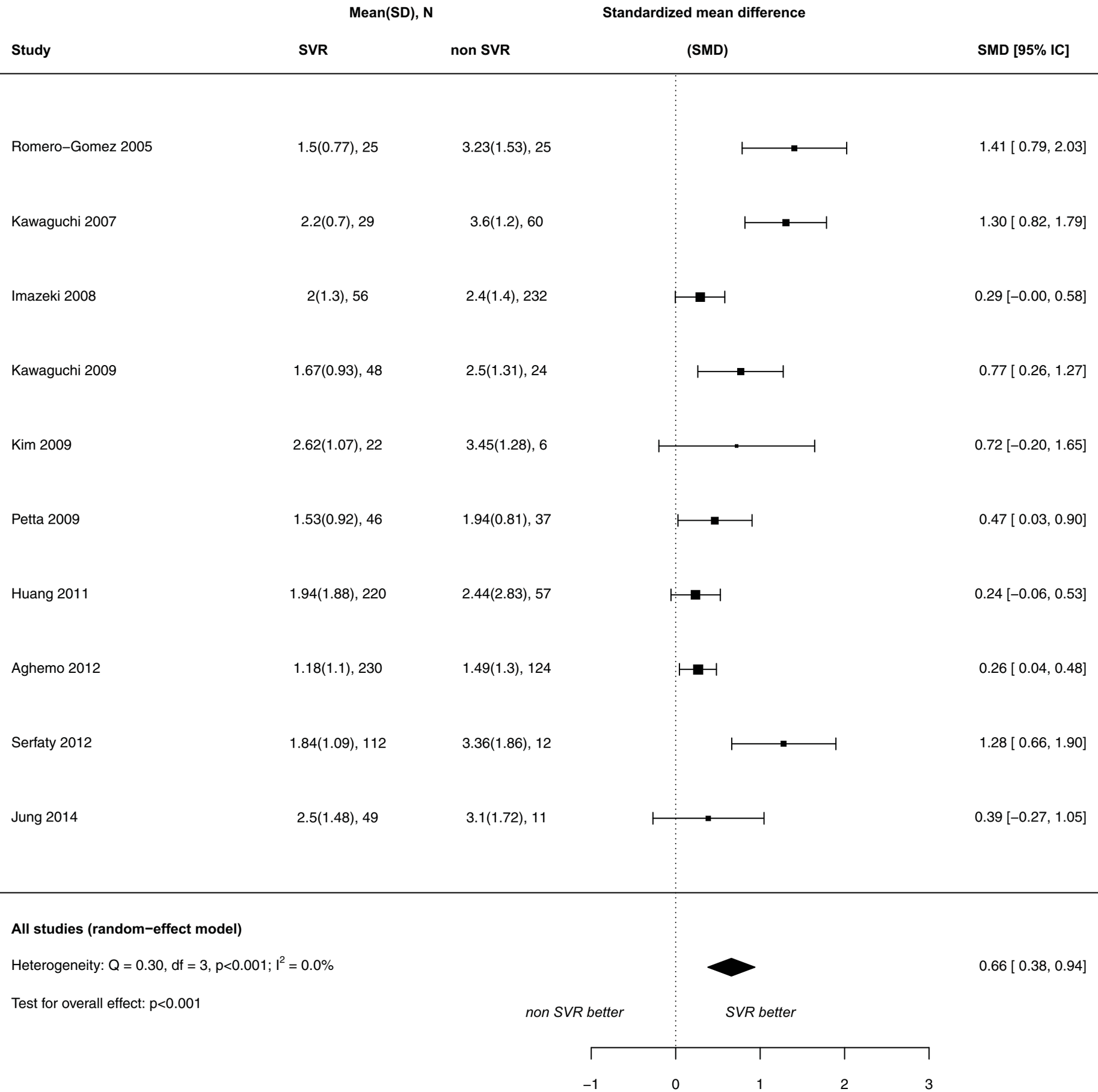

2270 Abstracts screened:
Embase + PubMed results
1886 Excluded
• Case reports
• Lack of data by SVR
• Lack of extrahepatic data
• Review articles
Added material
57 articles were obtained upon manual screening of recent meta-analyses.
498 Full-text articles read:
• 441 from Embase + PubMed
• 57 from additional sources
- 433 articles eliminated primarily due to missing comparator group data or incomplete reporting of SVR
- 2 articles were not possible to obtain.
- 15 articles eliminated due to missing specific outcome or same patients population reported in included studies.
48 publications included in meta-analyses

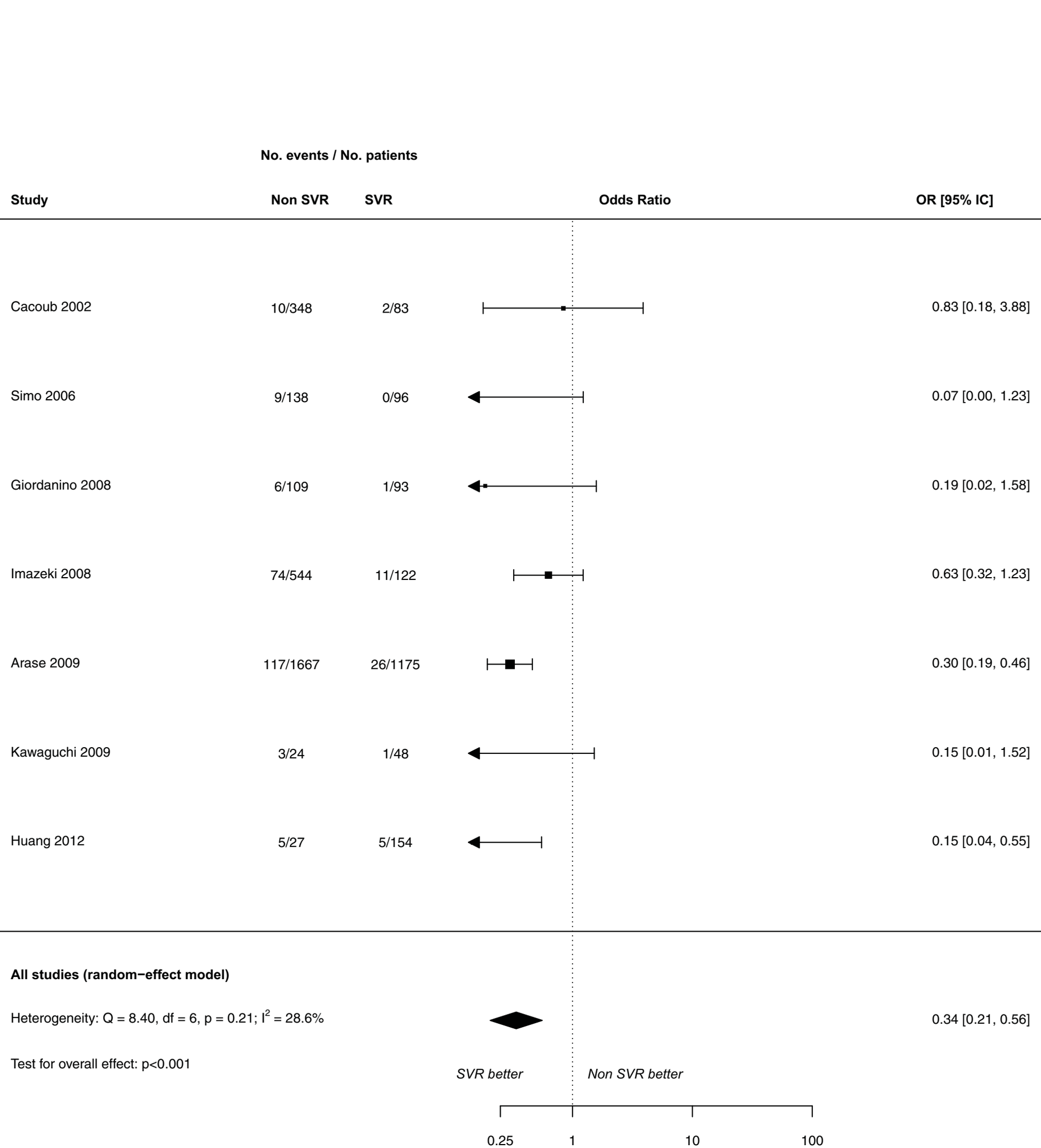

No. events / No. patients
Study
non SVR
SVR
Odds Ratio
OR [95% IC]
Cacoub 2002
0/4
0/9
0.47 [0.01, 27.94]
Martinez−Macias 2015
2/61
0/13
0.88 [0.04, 19.44]
Lin 2017
14/745
40/4564
0.46 [0.25, 0.85]
Nahon 2017
48/1014
13/665
0.40 [0.22, 0.75]
All studies (random−effect model)
Heterogeneity: Q = 0.30, df = 3, p = 0.96; I2 = 0.0%
Test for overall effect: p<0.001
0.44 [0.28, 0.67]
SVR better
non SVR better
0.25
1
10
100


No. events / No. patients
Study
SVR
non SVR
Odds Ratio
OR [95% IC]
Cacoub 2002
9/9
1/4
44.33 [1.44, 1365.06]
Mazzaro 2003
5/5
0/22
495.00 [8.80, 27828.82]
Mazzaro 2005
8/8
0/10
357.00 [6.39, 19942.80]
Saadoun 2006
33/42
12/30
5.50 [1.95, 15.52]
Joshi 2007
14/16
5/22
23.80 [3.99, 141.96]
Dammacco 2010
17/27
0/10
35.00 [1.85, 660.99]
Gragnani 2015
36/63
0/58
155.29 [9.19, 2624.33]
Malaguarnera 2015
15/15
0/9
589.00 [10.76, 32230.87]
Saadoun 2015
14/20
6/10
1.56 [0.32, 7.60]
Sise 2016 (1)
4/10
0/2
3.46 [0.13, 90.68]
Sise 2016 (2)
1/1
0/9
57.00 [0.79, 4123.85]
Bonacci 2017
24/33
1/2
2.67 [0.15, 47.30]
All studies (random−effect model)
20.76 [6.73, 64.05]
Heterogeneity: Q = 24.95, df = 11, p = 0.01;
I2 = 55.9%
Test for overall effect: p<0.001
non SVR better
SVR better
0.4
1
5
20
100


No. events / No. patients
Study
SVR
non SVR
Odds Ratio
OR [95% IC]
Mazzaro 2009
9/9
4/9
23.22 [1.04, 517.93]
Arcaini 2014
84/102
20/30
2.33 [0.94, 5.82]
Alric 2016 (1)
29/31
13/30
18.96 [3.81, 94.35]
Alric 2016 (2)
9/9
1/1
6.33 [0.09, 458.21]
Arcaini 2016
31/45
0/1
6.52 [0.25, 169.85]
All studies (random−effect model)
Heterogeneity: Q = 6.22, df = 4, p = 0.18; I2 = 35.7%
Test for overall effect: p = 0.0017
6.49 [2.02, 20.85]
non SVR better
SVR better
0.25
1
10
100


No. events / No. patients
Study
non SVR
SVR
Odds Ratio
OR [95% IC]
Imazeki 2008
126/232
20/56
0.47 [0.26, 0.86]
Petta 2009
7/37
4/46
0.41 [0.11, 1.52]
Aghemo 2012
24/124
25/230
0.51 [0.28, 0.93]
Thompson 2012
116/284
160/754
0.39 [0.29, 0.52]
All studies (random−effect model)
Heterogeneity: Q = 0.74, df = 3, p = 0.86; I2 = 0.0%
Test for overall effect: p<0.001
0.42 [0.33, 0.53]
SVR better
non SVR better
0.25
1
2
4


Mean(SD), N
Standardized mean difference
Study
SVR
non SVR
(SMD)
SMD [95% IC]
Romero−Gomez 2005
1.5(0.77), 25
3.23(1.53), 25
1.41 [0.79, 2.03]
Kawaguchi 2007
2.2(0.7), 29
3.6(1.2), 60
1.30 [0.82, 1.79]
Imazeki 2008
2(1.3), 56
2.4(1.4), 232
0.29 [−0.00, 0.58]
Kawaguchi 2009
1.67(0.93), 48
2.5(1.31), 24
0.77 [0.26, 1.27]
Kim 2009
2.62(1.07), 22
3.45(1.28), 6
0.72 [−0.20, 1.65]
Petta 2009
1.53(0.92), 46
1.94(0.81), 37
0.47 [0.03, 0.90]
Huang 2011
1.94(1.88), 220
2.44(2.83), 57
0.24 [−0.06, 0.53]
Aghemo 2012
1.18(1.1), 230
1.49(1.3), 124
0.26 [0.04, 0.48]
Serfaty 2012
1.84(1.09), 112
3.36(1.86), 12
1.28 [0.66, 1.90]
Jung 2014
2.5(1.48), 49
3.1(1.72), 11
0.39 [−0.27, 1.05]
All studies (random−effect model)
0.66 [0.38, 0.94]
Heterogeneity: Q = 0.30, df = 3, p<0.001; I2 = 0.0%
Test for overall effect: p<0.001
non SVR better
SVR better
−1
0
1
2
3


No. events / No. patients
Study
Non SVR
SVR
Odds Ratio
OR [95% IC]
Cacoub 2002
10/348
2/83
0.83 [0.18, 3.88]
Simo 2006
9/138
0/96
0.07 [0.00, 1.23]
Giordanino 2008
6/109
1/93
0.19 [0.02, 1.58]
Imazeki 2008
74/544
11/122
0.63 [0.32, 1.23]
Arase 2009
117/1667
26/1175
0.30 [0.19, 0.46]
Kawaguchi 2009
3/24
1/48
0.15 [0.01, 1.52]
Huang 2012
5/27
5/154
0.15 [0.04, 0.55]
All studies (random−effect model)
Heterogeneity: Q = 8.40, df = 6, p = 0.21; I2 = 28.6%
0.34 [0.21, 0.56]
Test for overall effect: p<0.001
SVR better
Non SVR better
0.25
1
10
100