Revised: 14 May 2019

# **ORIGINAL ARTICLE**

WILEY

# Direct-acting antivirals for HCV treatment in older patients: A systematic review and meta-analysis

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# Abstract

The advent of highly effective and well-tolerated direct antiviral antivirals (DAAs) has dramatically changed the landscape of chronic hepatitis C. The effect of DAAs in older adults is difficult to determine since patients aged ≥ 65 years were too few in most clinical trials and data mainly come from observational studies. We performed a systematic review and meta-analysis to evaluate the efficacy and safety of DAAs in patients aged 65 and older. PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, HCV-Trials.com databases were searched for literature published until 1 December 2017. English language articles reporting results of phase 2 or 3 randomized controlled trials (RCTs), single-arm clinical trials (SATs) and observational studies were included in the final analysis. All studies included subgroups of older patients and compared their outcomes with younger individuals. By using a random-effects or fixed-effects model, odds ratio (OR) was calculated for the efficacy and safety. Heterogeneity was tested using  $I^2$  statistics. Thirty-seven studies reported data on the DAA efficacy. The OR was 1.66 (95%CI: 1.00-2.75; P = 0.06) in meta-analysis of RCTs, and similar results were found in SATs and observational studies. HCV genotype, stage of fibrosis or HIV co-infection did not affect the rate of SVR in older persons. Prevalence of anaemia (OR 0.26 95%CI: 0.09-0.69; P = 0.007) (OR 0.25 95%CI: 0.09-0.69; P = 0.007) and skin complaints (OR 0.61 95%CI: 0.45-0.83; P = 0.001) was higher in older adults. Finally, geriatric patients affected by chronic HCV infection can be safely treated with DAAs with the same efficacy reported in younger adults.

# KEYWORDS

direct-acting antivirals, hepatitis C, older adults, viral hepatitis

# **1** | INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major cause of cirrhosis, hepatocellular carcinoma (HCC) and end-stage liver disease.<sup>1</sup> There are an estimated 2.4 million people living with hepatitis C in the United States. Approximately 75% of people with hepatitis C were born between 1945 and 1965 (Baby Boomers) with the oldest already 73 years old.<sup>2</sup> US national prevalence data show that people born during these years are five times more likely than other adults to be infected with HCV.

Cure of HCV infection defined as undetectable HCV RNA in the blood at least 12 weeks after treatment completion (SVR) strongly reduces the risk of liver-related morbidity and mortality.<sup>1,3</sup>

Abbreviations: CHC, Chronic Hepatitis C; DAA, Direct-acting Antivirals; RCT, Randomized Controlled Trials; SAT, Single-Arm Trials; SVR, Sustained Virological Response

The advent of highly effective and well-tolerated direct-acting antiviral agents (DAAs) has dramatically changed the landscape of chronic hepatitis C,<sup>4</sup> and the global rate of virological response is currently above 90% for most patients.<sup>5-12</sup>

Due to the absence of interferon and the short course of the treatment, an increasing number of patients are eligible for antiviral treatment, including older patients who generally do not tolerate interferon.<sup>4,13</sup> Observational data on HCV infection report that the prevalence of chronic hepatitis C (CHC) increases with age; in addition, older individuals often present with cirrhosis complications as initial manifestations of infection<sup>14,15</sup> and have higher liver-related mortality rate.<sup>15,16</sup>

These concerns suggest that treatment of HCV infection in older persons is an important public health intervention. However, the global efficacy of this new class of drugs is difficult to determine since patients aged  $\geq$  65 years were too few in most clinical trials and data mainly come from observational studies.

Accordingly, the present meta-analysis was aimed to assess the efficacy and the frequency of side effects of DAA treatment in older CHC patients compared to younger individuals.

# 2 | METHODS

This meta-analysis is reported according to the criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement<sup>17</sup> and the Cochrane handbook guidelines.<sup>18</sup>

#### 2.1 | Data sources and searches

We searched Pubmed, Web of Science, Scopus, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, HCV-Trials.com for literature published in English until 1 December 2017. We also checked the reference lists of included articles, review articles and meta-analyses identified by the electronic searches to find other eligible studies. The search strategy included terms for anti-HCV medications and target population. Relevant citations were retrieved after traditional screening of title and abstract.

The identification of relevant abstracts, the selection of studies based on the criteria described above were performed independently by two of the authors (RV and FDC), and conflicts resolved by a third investigator (MM).

# 2.2 | Study selection

We selected English language articles reporting results of:

- a) phase 2 or 3 randomized controlled trials (RCTs) evaluating different duration of treatment or same treatment duration with or without ribavirin or comparison including different antiviral regimens;
- b) single-arm clinical trials (SATs);
- c) observational studies (prospective or retrospective).

Older adults were defined as being 65 years and older compared to individuals < 65 years (adults).

Subgroup analysis of older adults over age 75 and 80 was also included. In the final analysis, only studies reporting efficacy and/or safety data by age subgroups were considered. Studies including older patients but reporting only overall results were excluded.

Studies assessing the efficacy of any oral DAA-containing combination (HCV NS3 protease and/or NS5A and/or NS5B polymerase inhibitors) for which the primary outcome was the sustained virological response (SVR) and/or side effect rates were included in the meta-analysis. SVR was defined as undetectable HCV RNA in the blood at least 12 weeks after therapy completion. Studies reporting interferon-containing regimens or non-FDA-approved drugs were excluded.

## 2.3 | Data extraction and quality assessment

Data extraction were performed independently by two of the authors (RV and FDC), and conflicts resolved by a third investigator (MM). Using standardized forms, the first investigator extracted data from the selected studies about design, outcomes, study characteristics, SVR rate and prevalence of side effects. A second investigator appraised the accuracy of the extractions. They independently assessed risk of bias for each study by using the Cochrane risk-of-bias tools for RCTs and the Cochrane tool for assessment of risk of bias in nonrandomized trials and observational studies.<sup>18,19</sup> The number of titles/abstracts identified, accepted and rejected was recorded. Adverse events were recorded and defined by using methods recommended by Cochrane Collaboration Guidelines.<sup>20</sup>

### 2.4 | Statistical analysis

Aggregate trial data were used for a quantitative synthesis (ie for calculation of endpoint mean and 95% Confidence Intervals for continuous variables, and Mantel-Haenzel Odds Ratio [MH-OR] for categorical variables). Both fixed and random effect models were applied. A sensitivity analysis with continuity correction, using random-effects models, was performed for categorical variables listed among principal endpoints. Heterogeneity between studies was evaluated using the  $l^2$  statistic with a cut-off point of  $\geq$  50%, and a *P* value < 0.10 on the chi-square test was defined as a significant degree of heterogeneity. Proportion meta-analysis was also performed to obtain a pooled SVR rate. Results were considered statistically significant at two-sided  $P \leq 0.05$ .

Publication bias was explored performing Egger's test, a contour enhanced funnel plot and trim and fill analysis, where there were more than 10 studies available.

Statistical analyses were performed using STATA (version 14; STATA Corporation) and Review Manager 5.1 (Cochrane Collaboration).



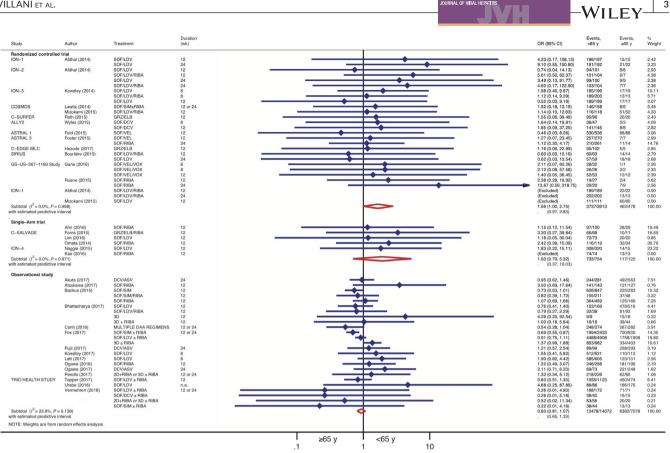


FIGURE 1 DAA efficacy in older adults compared to younger adults. Forest plot for OR and corresponding 95% confidence intervals (CIs)

#### 3 RESULTS

#### Study and quality characteristics 3.1

Starting from 13 721 citations, a total of 37 studies were included in the final analysis to explore the efficacy outcome (13 RCTs, 6 SATs and 18 observational studies); 10 of these studies were used for the analysis of safety.

Study characteristics and the PRISMA flow chart are shown in Table S1 and Figure S1, respectively.

Seven observational studies also included a subgroup analysis of patients over 75 years <sup>13,21-26</sup>; one observational study and one SAT reported data on patients older than 80 years.<sup>21,27</sup>

Safety outcomes were reported by 10 studies (1 RCT, 1 SAT and 8 observational studies).<sup>10,13,22-25,28-31</sup> The risk of bias of the included studies is shown in Table S2 and S3.

Among RCTs and SATs, six had high risk in blinding of participants and personnel and one study had high risk for selective reporting of outcomes. The risk of bias of observational studies was globally low.

Potential sources of bias included single-group design; since SVR is a highly objective measurement of treatment, lack of blinding was not considered relevant.

Statistical assessment of publication bias using a contour enhanced funnel plots showed symmetry and suggested the absence of significant publication bias (Figure S2). The Egger's test and the trim and fill analysis were not statistically significant, indicating that publication bias had no effects on the final results.

# 3.2 | Meta-analysis of RCTs: Efficacy of DAAs in adults aged $\geq$ 65 years

Thirteen RCTs comprising 3913 adults and 478 older adults were included in our final analysis. In the overall analysis, no differences were found between older adults and adults treated with DAAs [OR 1.66 (95%CI: 1.00-2.75; P = 0.06; I<sup>2</sup> = 0%)] (Figure 1). Very interestingly, in all studies no difference was found between the two age subgroups. Only one study showed that the efficacy of DAAs was higher in older adults.<sup>32</sup>

Proportion meta-analysis showed a pooled SVR rate of 98.5% in the older population.

Sustained Virological Response rates were not significantly different between young and old patients independently from HCV genotype.

Eight RCTs reported SVR rate for genotype G1 in older adults (Table S4). DAA regimens included sofosbuvir/ledipasvir with or without ribavirin, 5,6,10,12,33 sofosbuvir/velpatasvir, 11 grazoprevir/elbasvir<sup>34</sup> and sofosbuvir plus simeprevir<sup>8</sup> were analysed.

The OR was 1.29 (95%CI: 0.64-2.59; P = 0.48) and pooled SVR rate was 99%.

Data on genotype 2 HCV patients over 65 years were very limited and included in only one RCT with 25 patients treated with sofosbuvir/velpatasvir and an SVR of 100%.<sup>11</sup>

Only one open-label phase 3 study included genotype 3-infected patients: Seven were treated with sofosbuvir/velpatasvir and 14 with sofosbuvir plus ribavirin. The response rates were 100% and 78.6%, respectively.<sup>35</sup>

Two RCTs were published on genotype 4 infected patients (Table S5). One included 11 patients treated with sofosbuvir/velpatasvir for 12 weeks and an SVR of 100%<sup>11</sup>; the second included 13 patients treated with sofosbuvir and ribavirin for 12 or 24 weeks (overall SVR 77.8%).<sup>36</sup>

One phase 3 RCT included 11 HIV/HCV patients treated with sofosbuvir and daclatasvir. No difference between younger and older patients was observed (OR 1.18; 95%CI 0.14-9.85).<sup>37</sup>

# 3.2.1 | Patients with cirrhosis

Data on the efficacy of DAA treatment in older cirrhotic patients were reported in a Phase 3 Open-label Multicenter RCT enrolling 7 patients; all of them achieved SVR.<sup>38</sup>

# 3.3 | Efficacy of direct-acting antivirals in adults aged ≥ 65 years: Results from meta-analysis of SATs

Six single-arm trials were considered (754 adults and 122 older adults) and the final result confirmed the meta-analysis of RCTs (OR 1.93 95%CI 0.70-5.32; P = 0.21;  $I^2$  0%): HCV G1-2-4 infected elderly patients had SVR rates comparable with adults (Figure 1).

# 3.4 | Meta-analysis of observational studies: Efficacy of DAAs in adults aged ≥ 65 years

Eighteen observational studies comprising 14 072 adults and 7078 older adults were included in the meta-analysis, and no difference was observed between elderly and adults SVR rate [OR was 0.93 (95%Cl 0.81-1.07; P = 0.33;  $I^2$  24%)] (Figure 1); proportion meta-analysis showed a pooled SVR rate of 92.4%.

Seven studies comprising 3136 patients compared DAAs efficacy in a subgroup of patients  $\geq$  75 years and demonstrated no difference in terms of OR compared to patients < 75 years.

Two studies also reported data on a total of 333 patients  $\ge$  80 years and no OR difference was observed when compared to < 80 years old.

The influence of HCV genotype in terms of SVR was also explored in the observational studies.

Eight observational studies reported SVR of HCV genotype 1 in older adults (n = 2824) compared to adults (n = 3994), and no significant difference was observed (OR 1.01; 95%CI: 0.80-1.27; P = 0.94).<sup>21,25,39-44</sup>

The OR in older G2 HCV infected patients was not significantly different from adults (OR = 1.17; 95%CI: 0.81-1.69; P = 0.96).

No data on SVR of older patients infected with G4 were found, and only one retrospective cohort study included three patients with G3 HCV.

A large retrospective study conducted in the US reported data on 234 HCV/HIV<sup>+</sup> patients aged  $\geq$  65 years treated with DAAs; SVR was not significantly different between older patients and adults (OR 1.21; 95%CI 0.22-1.99).<sup>40</sup>

# 3.4.1 | Cirrhotic patients ≥ 65 years

The analysis of cirrhotic patients was reported in three observational studies including 397 patients  $\geq$  65 years; the SVR rate was 91.9% in older cirrhotic patients vs 89.5% of cirrhotic adults with no difference in terms of OR (OR = 1.32, 95%CI: 0.49-3.57; *P* = 0.58; *I*<sup>2</sup> = 41.5%) (Figure S3).<sup>23-25</sup>

# 3.5 | Safety of DAA treatment in adults aged $\geq$ 65 years

The prevalence of 'any adverse events', 'anaemia', 'skin complaints' and 'neurological or psychiatric symptoms' was statistically different between adults and older adults (Figure 2). The crude rates for adverse events in adults aged  $\ge$  65 years are reported in Table S6.

In the overall analysis, anaemia was more frequently observed in older individuals compared to adults (22.7% vs 9.4%; OR 0.25 95%CI: 0.09-0.69; P = 0.007). It is interesting to note that a significant proportion of older adults enrolled in studies reporting anaemia received ribavirin in the antiviral regimen (49.8%).

When the analysis was limited to a subgroup of studies enrolling only older patients with ribavirin combination treatment, <sup>22,24,28</sup> the OR was 0.14 (95%CI: 0.06-0.32; P = 0.0001) as compared to adults. (4.6%). Unfortunately, no studies reported the prevalence of anaemia in older adults treated with DAAs without ribavirin.

Seven studies reported data on the prevalence of skin complaints in different age subgroups and reported a slight increase in the frequency of pruritus, rash and photosensitivity in patients aged  $\geq$  65 years (7% vs 9.9%; OR 0.61 95%CI: 0.45-0.83; P = 0.001).<sup>10,13,22-24,28,29</sup> To verify the impact of protease inhibitors in the prevalence of skin complaints in older adults, a subgroup analysis only including patients without protease inhibitors<sup>10,22,24,28</sup> in the antiviral regimen was performed and we did not observe any significant difference (OR 0.62 95%CI: 0.31-1.26; P = 0.19).

Neurological or psychiatric symptoms included headache, dizziness, insomnia and depression were reported in five observational studies. The overall prevalence was 6.3% in older adults and 14.7% in adults (3.3% vs 4.6%; OR 1.70 95%CI: 1.16-2.49; P = 0.006).

Three observational studies reported on the prevalence of gastrointestinal side effects (nausea, abdominal pain, vomiting, diarrhoea, constipation, ischaemic colitis and haemorrhagic gastric ulcer) and showed no difference in the age subgroups (2.8% in adults versus 2.3% in older people).<sup>22,23,29</sup>

Five studies reported data on the risk of DAA discontinuation in patients of different ages: it was observed in 0.9% and 1.2% of

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| Schell Sind     0.51 (10.00, 0.8h]     32.66       Stackar 2015     2.77 (10.25, 19.4)     1.82       Syma 3014     0.37 (0.27, 1.96)     9.44       Dask 3014     0.37 (0.27, 1.96)     9.44       Dask 3014     0.37 (0.27, 1.96)     9.44       Dask 3014     0.57 (0.27, 1.96)     9.44       Dask 3014     0.57 (0.27, 1.96)     9.44       Dask 3014     0.57 (0.27, 1.96)     9.47       Meetineed predictive interval     0.61 (0.45, 0.81)     100.00       Stackar 2017     1.66 (0.45, 4.87)     1.72       Stackar 2017     1.16 (0.41, 4.47)     8.27       Stackar 2017     1.16 (0.41, 4.47)     8.27       Stackar 2017     1.16 (0.41, 4.47)     1.86       Stackar 2017     1.16 (0.41, 2.87)     1.82       Stackar 2017     1.16 (0.41, 2.87)     1.82       Stackar 2017     1.16 (0.41, 2.87)     1.82       Stackar 2017     1.16 (0.43, 2.87)     1.92       Stackar 2016     1.72 (0.16, 2.49)     1.92       Stackar 2016     1.92     1.92       Stackar 2016   | Skin complaints                                    |                    |             |
| dtsdam 2015     2.47 (1.0.2, 0.1.9.4)     1.02       gyna 2016     2.47 (1.0.2, 0.1.9.4)     9.44       bring 2017     0.73     0.74       bring 2017     0.74     0.72, 0.22, 1.99     9.44       bring 2017     0.74     0.73     0.73     0.83 (0.03, 1.03)     9.73       bring 2016     bring 2016     0.63 (0.03, 1.03)     0.73     0.63 (0.03, 1.03)     9.73       bring 2016     bring 2016     0.63 (0.03, 1.03)     1.64     0.73     0.63 (0.03, 1.03)     1.62       bring 2017     4.51 (0.2, 19, 0.73)     1.52   |  |                    |             |
| Spans 2016     0.73 (0.27, 1.99-1     9, 44       Inviso 2014     0.73 (0.27, 1.99-1     9.44       Inviso 2017     0.73 (0.27, 1.99-1     9.79       Inviso 2016     0.73 (0.27, 1.99-1     9.79       Inviso 2017     0.73 (0.27, 1.99-1     9.79       Inviso 2016     0.73 (0.27, 1.99-1     9.79       Inviso 2016     0.73 (0.27, 1.99-1     9.79       Inviso 2017     0.63 (0.03, 1.00)     10.20       Inviso 2016     1.16 (0.46, 2.67)     1.724       Inviso 2016     1.16 (0.46, 2.67)     1.724       Inviso 2016     1.12 (0.60, 2.79)     1.14       Inviso 2017     1.15 (0.46, 2.87)     1.126       Inviso 2017     1.16 (0.44, 2.06)     20.81       Inviso 2017     1.86 (0.06, 1.43)     8.86       Inviso 2017     1.86 (0.24, 1.06, 2.79)     1.100       Inviso 2017     1.86 (0.24, 1.06, 2.79)     1.100       Inviso 2017     1.96 (0.02, 1.13)     8.86       Inviso 2017     1.96 (0.02, 1.13)     1.81       Inviso 2017     1.96 (0.02, 1.15)     1.81       In  | •  |                    |             |
| Name 2014     0.33 (00.1.90)     4.88       Honge 2017     0.78 (0.28, 207)     5.79       Harmshein 2016     0.65 (0.28, 1.00)     27.33       Harmshein 2016     0.65 (0.28, 1.00)     27.33       Harmshein 2016     0.65 (0.28, 1.00)     27.34       Harmshein 2016     0.61 (0.45, 0.65)     100.00       Harmshein 2017     4.51 (0.21, 94.70)     1.46       Harmshein 2016     1.16 (0.43, 4.57)     8.27       Harmshein 2016     1.17 (1.16, 2.39)     1.16       Harmshein 2016     1.16 (0.41, 0.18)     1.16   |  |                    |             |
| balage 2017<br>transfer 2016<br>transfer 2016<br>the standard predictive interval<br>the standard predictive interva   | Dgawa 2016   | 0.73 (0.27, 1.99)  | 9.44        |
| immaken 2016     0.58 (0.83, 1.03)     97.33       ide settimated prodictive interval     0.58 (0.85, 0.03)     100.00       ide settimated prodictive interval     0.58 (0.85, 0.03)     156       ide settimated prodictive interval     0.58 (0.85, 0.03)     156       ide settimated prodictive interval     1.56     1.56 (0.82, 97)     156       intervalue of (* 0.57, 8 - 0.50)     1.72 (1.66, 2.79)     15.46       intervalue of (* 0.57, 8 - 0.50)     1.72 (1.66, 2.79)     15.46       intervalue of (* 0.57, 8 - 0.50)     1.72 (1.66, 2.79)     15.47       intervalue of (* 0.57, 8 - 0.50)     1.72 (1.66, 2.79)     15.48       intervalue of (* 0.57, 8 - 0.50)     1.72 (1.66, 2.79)     15.48       intervalue of (* 0.57, 8 - 0.50)     1.72 (1.66, 2.79)     15.48       intervalue of (* 0.57, 8 - 0.50)     1.56 (1.13)     10.50       intervalue of (* 0.57, 8 - 0.50)     1.58 (1.13)     10.50       intervalue of (* 0.57, 1.31)     0.59 (0.51, 1.33)     10.50       intervalue of (* 0.57, 1.31)     0.59 (0.51, 1.33)     10.50       intervalue of (* 0.57, 1.57)     10.50     1.58 (1.71)     10.50  |  |                    |             |
| backball (***********************************  |  | 0.78 (0.29, 2.07)  | 9.79        |
| ath administed predictive interval   . (0.41, 0.91)     teuro log(cal or psychiatric symptoms<br>statisticans 2017<br>Link data 2016<br>Interval 2016<br>ath administed predictive interval   4     Statisticans 2017<br>Link data 2016<br>Interval administer interval   4     Statisticans 2017<br>Link data (1.437)   8.22<br>Link data (1.437)     Statisticans 2017<br>Link data (1.437)   8.23<br>Link data (1.437)     Statisticans 2016<br>Link data (1.437)   8.86<br>Link data (1.437)     Statisticans 2017<br>Link data (1.437)   4.16 (0.00, 0.187)     Statisticans 2017<br>Link data (1.437)   4.16 (0.00, 0.187)     Statisticans 2017<br>Link data (1.437)   4.16 (0.00, 0.185)     Statisticans 2017<br>Link data (1.437)   4.16 (0.00, 0.158)     Statisticans 2017<br>Link data (1.437)   |  | 0.63 (0.38, 1.03)  | 37.33       |
| taukana 2017     4.51 (2.1, 94.7.3)     1.56       hanga 2014     1.16 (0.3, 1.4, 3.7)     8.22       hanga 2014     1.16 (0.3, 1.4, 3.7)     8.22       hanga 2017     1.26 (0.5, 2.7)     1.12 (1.0, 2.7)     6.1.48       hanga 2016     1.72 (1.0, 2.49)     10.000     1.72 (1.0, 2.49)     10.000       hanga 2017     0.88 (0.5, 1.43)     8.86     1.70 (1.10, 2.49)     10.000       hanga 2017     0.88 (0.5, 1.43)     8.86     1.81 (0.40, 0.91)     8.86       hanga 2017     0.88 (0.5, 1.43)     8.86     1.16 (0.40, 0.91)     8.76       hanga 2017     0.88 (0.5, 1.43)     8.86     1.81 (0.40, 0.91)     2.76       hanga 2017     0.88 (0.5, 1.43)     8.86     1.82 (0.70, 3.75)     10.00       hanga 2017     0.88 (0.5, 1.13)     0.50     1.82 (0.70, 3.75)     10.50       hanga 2017     0.90 (0.5, 1.53)     1.53     1.53     1.53       hanga 2017     0.90 (0.5, 1.53)     1.53     1.53     1.53       hanga 2017     0.90 (0.5, 1.53)     1.53     1.53       hanga 2017   | Subtotal $(I^2 = 0.0\%, P = 0.854)$                | 0.61 (0.45, 0.83)  | 100.00      |
| stackwa 2017   451 (0 21, 94.79)   1.56     ionik 2016   1.15 (0.46, 2.87)   1.72 (1.15 (2.19, 1.27)     ihanda 2014   1.15 (0.46, 2.87)   1.72 (1.15 (2.29)   11.80     ihanda 2014   1.72 (1.16 2.29)   11.80  | vith estimated predictive interval                 | . (0.41, 0.91)     |             |
| Some 2016   1.15 (0.44, 2.87)   1.72 (4.16, 1.22)     Minta 2014   1.15 (0.47, 1.47)   8.27     Marka 2017   1.72 (1.06, 2.79)   61.48     Muta 2014   | Neurological or psychiatric symptoms               |                    |             |
| Inite 2014   116 (0.31, 4.27)   8.22     heing 2017   3.33 (1.06, 10.22)   11.50     interation 2016   1.72 (1.16, 2.79)   61.48     interation complaints   1.70 (1.16, 2.49)   100.00     saturines interval   0.89 (0.05, 14.33)   8.86     interval   0.89 (0.05, 14.33)   8.86     interval   1.16 (0.44, 0.00)   63.18     heing 2017   0.89 (0.05, 14.33)   8.86     interval   1.16 (0.44, 0.00)   63.18     interval   1.16 (0.47, 0.37)   100.00     interval   1.16 (0.47, 0.37)   100.00     interval   0.87 (0.57, 1.31)   40.50     interval   0.87 (0.57, 1.31)   40.50     interval   0.70 (0.86, 1.55)   15.33     interval   0.70 (0.86, 1.55)   15.33     interval   0.70 (0.86, 1.55)   15.46     interval   0.50 (0.02, 0.15)   18.46     interval   0.50 (0.02, 0   | Atsukawa 2017                                      | 4.51 (0.21, 94.73) | 1.56        |
| bedgar 2017<br>immateran 2016<br>bubboal (f = 0.05%, F = 0.590)<br>ath estimated predictive interval<br>Statkwa 2017<br>coni 2016<br>bubboal (F = 0.5%, F = 0.439)<br>ath estimated predictive interval<br>Cong 2016<br>bubboal (F = 0.5%, F = 0.439)<br>ath estimated predictive interval<br>Cong 2016<br>bubboal (F = 0.5%, F = 0.439)<br>ath estimated predictive interval<br>Cong 2016<br>bubboal (F = 0.5%, F = 0.437)<br>the estimated predictive interval<br>Cong 2016<br>bubboal (F = 0.5%, F = 0.439)<br>ath estimated predictive interval<br>Cong 2016<br>bubboal (F = 0.5%, F = 0.437)<br>the estimated predictive interval<br>Cong 2016<br>bubboal (F = 0.5%, F = 0.407)<br>the estimated predictive interval<br>Cong 2016<br>bubboal (F = 0.5%, F = 0.407)<br>the estimated predictive interval<br>Cong 2016<br>bubboal (F = 8.3%, F = 0.000)<br>ath estimated predictive interval<br>Cong 2016<br>bubboal (F = 8.3%, F = 0.000)<br>ath estimated predictive interval<br>Cong 2016<br>bubboal (F = 8.3%, F = 0.000)<br>ath estimated predictive interval<br>Cong 2016<br>bubboal (F = 8.3%, F = 0.000)<br>ath estimated predictive interval<br>Cong 2016<br>bubboal (F = 8.3%, F = 0.000)<br>ath estimated predictive interval<br>Cong 2016<br>bubboal (F = 8.3%, F = 0.000)<br>ath estimated predictive interval<br>Cong 2016<br>bubboal (F = 8.3%, F = 0.000)<br>ath estimated predictive interval<br>Cong 2016<br>bubboal (F = 8.3%, F = 0.000)<br>ath estimated predictive interval<br>Cong 2016<br>Cong 2016   | Conti 2016   | 1.15 (0.46, 2.87)  | 17.24       |
| termstern 2016   1.72 (1.06, 2.79)   61.48     ubotal ( $f^2$ = 0.0%, P = 0.560)   1.72 (1.16, 2.49)   100.00     astrointestinal complaints   (0.82, 3.15)   0.89 (0.05, 14.33)   8.86     taskakana 2017   0.89 (0.05, 14.33)   8.86   0.81 (0.90, 0.93)   0.81 (0.90, 0.93)     biologic 2017   0.89 (0.05, 14.33)   8.86   0.81 (0.90, 0.93)   0.90 (0.90, 14.30)   8.86     taskakana 2017   0.89 (0.05, 14.33)   8.86   0.89 (0.05, 14.33)   8.86     taskakana 2017   1.82 (0.70, 3.77)   100.00   0.90 (0.90, 1.83)   1.82 (0.70, 3.75)   100.00     cons 2016   0.70 (0.36, 1.35)   16.33   0.99 (0.60, 1.35)   16.33     taskakana 2017   0.95 (0.95, 1.10)   10.00   0.90 (0.60, 1.37)   22.99     taskakana 2017   0.90 (0.60, 1.37)   22.99   0.90 (0.60, 1.37)   22.99     taskakana 2017   0.91 (0.00, 0.99)   20.88   0.22 (0.02, 0.91)   10.00     taskakana 2017   0.91 (0.00, 0.93)   20.88   0.22 (0.02, 0.91)   10.90     taskakana 2017   0.92 (0.60, 1.37)   22.89   0.92 (0.61, 1.37)   23.93     tab  | Dmata 2014   | 1.16 (0.31, 4.37)  | 8.22        |
| ubtobal ( $l^2 = 0.05, P = 0.590$ )   1.70 (1.16, 2.49)   100.00     startonizetinal complaints   . (0.92, 3.15)   . (0.92, 3.15)     startonizetinal complaints   1.16 (0.44, 3.06)   63 18     sonig 2017   1.16 (0.44, 3.06)   63 18     ubtobal ( $l^2 = 55, P = 0.343$ )   4.16 (0.30, 19.16)   2.246     ubtobal ( $l^2 = 0.05, P = 0.343$ )   . (0.00, 688.73)   . (0.00, 688.73)     ubtobal ( $l^2 = 0.05, P = 0.343$ )   . (0.70, (0.36, 1.35))   16 33     ubtobal ( $l^2 = 0.05, P = 0.343$ )   . (0.00, 688.73)   . (0.00, 688.73)     ubtobal ( $l^2 = 0.05, P = 0.343$ )   . (0.00, 688.73)   . (0.00, 688.73)     ubtobal ( $l^2 = 0.05, P = 0.343$ )   . (0.55, 1.13)   100.00     ubtobal ( $l^2 = 0.05, P = 0.343$ )   . (0.55, 1.13)   100.00     ubtobal ( $l^2 = 0.05, P = 0.343$ )   . (0.15, 4.37)   18.33     ubtobal ( $l^2 = 0.05, P = 0.807$ )   . (0.15, 4.37)   . (0.15, 4.37)     ubtobal ( $l^2 = 0.05, P = 0.807$ )   . (0.15, 4.37)   . (0.15, 4.37)     ubtobal ( $l^2 = 83.55, P = 0.000$ )   . (0.01, 10.54)   . (0.11, 0.54)     ubtobal ( $l^2 = 83.55, P = 0.000$ )   . (0.01, 10.54)   . (0.01, 10.54)     ubtobal ( $l^2 = 83.55, P = 0.016$ ) <td>Sherigar 2017</td> <td>3.33 (1.08, 10.22)</td> <td>11.50</td>   | Sherigar 2017                                      | 3.33 (1.08, 10.22) | 11.50       |
| attenting predictive interval   . (0.92, 3.15)     Asstrointestinal complaints   0.89 (0.05, 14.33)   8.86     toxiday 2017   1.16 (0.44, 3.06)   63.18     heighar 2017   1.16 (0.44, 3.06)   63.18     subtoal ( $1^2 = 6.5\%, P = 0.343$ )   1.16 (0.44, 3.06)   63.18     int estimated predictive interval   1.16 (0.44, 3.06)   63.18     Particular   0.89 (0.05, 14.33)   8.86     int estimated predictive interval   1.16 (0.44, 3.06)   63.18     Particular   0.87 (0.57, 1.31)   40.50     int estimated predictive interval   0.87 (0.57, 1.31)   40.50     Particular   0.87 (0.57, 1.31)   40.50     int estimated predictive interval   0.87 (0.57, 1.31)   40.50     Particular   0.87 (0.57, 1.31)   40.50     int estimated predictive interval   0.57 (0.57, 1.31)   40.50     Normal   0.57 (0.57, 1.31)   40.50   16.82     Statistical predictive interval   0.57 (0.57, 1.31)   40.50   16.82     Normal   0.57 (0.57, 1.31)   40.50   16.82   16.82   16.82     Statital 2017   0.56 (0.60, 1.37) <t< td=""><td>/ermehren 2016</td><td>1.72 (1.06, 2.79)</td><td>61.48</td></t<>   | /ermehren 2016                                     | 1.72 (1.06, 2.79)  | 61.48       |
| Sate/Initial complains     0.89 (0.05, 14.33)     8.86       Stakkawa 2017     1.16 (0.44, 3.06)     63.18       Yang 2016     1.16 (0.44, 3.06)     63.18       Haringar 2017     1.16 (0.59, 8.7 = 0.348)     1.16 (0.79, 3.75)     1.000       Yang 20     0.89 (0.05, 14.33)     8.86     1.16 (0.79, 3.75)     1.000       Yang 20     0.89 (0.05, 14.31)     40.50     0.70 (0.35, 1.55)     1.000     1.000     1.000 (0.00, 1.55)     43.17       Yang 2016     0.87 (0.57, 1.31)     40.50     0.59 (0.00, 1.55)     43.17       Yang 2016     0.87 (0.57, 1.31)     100.00     1.000   | Subtotal $(I^2 = 0.0\%, P = 0.590)$                | 1.70 (1.16, 2.49)  | 100.00      |
| stackava 2017   0.89 (0.05, 14.33)   8.86     Cond 2016   1.16 (0.44, 3.06)   63.18     berigar 2017   4.16 (0.90, 19.16)   27.96     subtotal ( $I^2$ = 0.5%, P = 0.343)   1.62 (0.70, 3.75)   100.00     ath estimated predictive interval   0.87 (0.57, 1.31)   40.50     berigar 2017   0.70 (0.36, 1.35)   16.33     berigar 2017   0.70 (0.36, 1.35)   16.33     fargue   0.87 (0.57, 1.31)   40.50     berigar 2017   0.70 (0.36, 1.35)   16.33     farmethen 2016   0.87 (0.57, 1.31)   40.50     batotal ( $I^2$ = 0.0%, P = 0.807)   1.62 (0.70, 3.75)   16.33     the estimated predictive interval   0.87 (0.57, 1.31)   100.00     stackawa 2017   0.90 (0.80, 1.37)   2.38     bargar 2017   0.90 (0.80, 1.37)   2.38     bargar 2016   0.90 (0.80, 0.39)   20.88     bargar 2017   0.39 (0.80, 0.39)   20.88     bargar 2017   0.39 (0.80, 0.39)   20.88     bargar 2016   0.90 (0.80, 1.37)   2.38     bargar 2017   0.39 (0.80, 0.39)   2.088     bargar 2016   | vith estimated predictive interval                 | . (0.92, 3.15)     |             |
| stackava 2017   0.89 (0.05, 14.33)   8.86     Cond 2016   1.16 (0.44, 3.06)   63.18     berigar 2017   4.16 (0.90, 19.16)   27.96     subtotal ( $I^2$ = 0.5%, P = 0.343)   1.62 (0.70, 3.75)   100.00     ath estimated predictive interval   0.87 (0.57, 1.31)   40.50     berigar 2017   0.70 (0.36, 1.35)   16.33     berigar 2017   0.70 (0.36, 1.35)   16.33     fargue   0.87 (0.57, 1.31)   40.50     berigar 2017   0.70 (0.36, 1.35)   16.33     farmethen 2016   0.87 (0.57, 1.31)   40.50     batotal ( $I^2$ = 0.0%, P = 0.807)   1.62 (0.70, 3.75)   16.33     the estimated predictive interval   0.87 (0.57, 1.31)   100.00     stackawa 2017   0.90 (0.80, 1.37)   2.38     bargar 2017   0.90 (0.80, 1.37)   2.38     bargar 2016   0.90 (0.80, 0.39)   20.88     bargar 2017   0.39 (0.80, 0.39)   20.88     bargar 2017   0.39 (0.80, 0.39)   20.88     bargar 2016   0.90 (0.80, 1.37)   2.38     bargar 2017   0.39 (0.80, 0.39)   2.088     bargar 2016   | Gastrointestinal complaints                        |                    |             |
| Sortil 2016   1.16 (0.44, 3.06)   63.18     herigar 2017   4.16 (0.29, 0.19.16)   27.96     situloal (1 <sup>2</sup> = 5%, P = 0.343)   1.62 (0.70, 3.75)   100.00     affigee   0.87 (0.57, 1.31)   40.50     Sortil 2016   0.87 (0.57, 1.31)   40.50     bergar 2017   0.97 (0.53, 1.35)   16.33     remehren 2016   0.97 (0.57, 1.31)   40.50     stutoal (1 <sup>2</sup> a - 0.0%, P = 0.807)   0.98 (0.60, 1.35)   143.17     stutoal (1 <sup>2</sup> a - 0.0%, P = 0.807)   0.98 (0.65, 1.11)   100.00     aft estimated predictive interval   - (0.15, 4.73)   -     Nemaia   0.56 (0.02, 0.15)   18.46     Sortil 2016   0.90 (0.60, 1.37)   22.39     Sortil 2016   0.90 (0.60, 1.37)   22.39     Sortil 2016   0.90 (0.60, 1.37)   22.39     Sortil 2016   0.90 (0.60, 1.37)   19.33     Sortil 2017   0.38 (0.6.07)   19.83     Sortil 2016   0.90 (0.60, 1.37)   35.85     Sortil 2016   0.45 (0.27, 0.75)   35.85     Sortil 2016   0.45 (0.27, 0.75)   35.85     Sortil 2016   0.47 (0.31  |  | 0.89 (0.05, 14,33) | 8.86        |
| herigar 2017   4.16 (0.90, 19.16)   27.96     subtoal (1 <sup>2</sup> = 6.5%, P = 0.343)   1.52 (0.70, 3.75)   100.00     if destinated predictive interval   .   (0.00, 698.73)   .     ratigue   .   .   (0.00, 698.73)   .     soft 2016   0.87 (0.57, 1.31)   40.50   .   .   .     storted (1 <sup>2</sup> = 0.0%, P = 0.87)   0.90 (0.60, 1.35)   16.33   .  | · · · · · · · · · · · · · · · · · · ·              |                    |             |
| babbcal (l <sup>2</sup> = 6.5%, P = 0.343)   1.62 (0.70, 3.75)   100.00     ath estimated predictive interval   . (0.00, 698.73)   . (0.00, 698.73)     Satigue   0.87 (0.57, 1.31)   40.50     Sordi 2016   0.87 (0.57, 1.31)   40.50     Settingue 7017   0.90 (0.60, 1.35)   43.31     Similar 2016   0.90 (0.60, 1.35)   43.17     Subtoal (l <sup>2</sup> = 0.0%, P = 0.807)   0.88 (0.65, 1.11)   100.00     ift estimated predictive interval   . (0.15, 4.73)   22.39     Subtoal (l <sup>2</sup> = 0.0%, P = 0.807)   0.90 (0.60, 1.37)   22.39     Sordi 2016   0.90 (0.60, 1.37)   22.39     Symata 2017   0.90 (0.60, 0.177)   22.39     Subtoal (l <sup>2</sup> = 0.57)   18.43   31.73     Stackaray 2017   0.90 (0.60, 0.177)   22.39     Symata 2014   0.23 (0.80, 0.69)   18.73     Statistad predictive interval   . (0.01, 10.54)   18.73     Statistad (l <sup>2</sup> = 7.75, 75, P = 0.000)   31.31   25.85     Statistad predictive interval   . (0.01, 10.54)   31.13     Statistad (l <sup>2</sup> = 7.75, P, P = 0.018)   0.41 (0.20, 0.84)   100.00     Statistad (l <sup>2</sup> = 7.75,   |  |                    |             |
| at set mated predictive interval   0.000.988.73)     at set mated predictive interval   0.87 (0.57, 1.31)   40.50     bini 2016   0.70 (0.36, 1.55)   16.33     0.90 (0.60, 1.35)   43.17   30.60     3thordal ( $I^2$ 0.0%, $P = 0.807$ )   0.88 (0.65, 1.11)   100.00     it estimated predictive interval   0.90 (0.60, 1.37)   22.39     Namela   0.90 (0.60, 1.37)   22.39     Stackawa 2017   0.55 (0.02, 0.15)   18.46     Soni 2016   0.90 (0.60, 1.37)   22.39     Mata 2014   0.39 (0.66, 1.37)   22.39     Shada 2014   0.39 (0.61.60, 77)   19.53     Shada 2015   0.93 (0.61.60, 77)   19.53     Shada 2016   0.90 (0.60, 1.37)   22.39     Shada 2014   0.39 (0.61.60, 77)   19.53     Shada 2014   0.39 (0.61.60, 77)   19.53     Shada 2015   0.52 (0.09, 0.69)   100.00     Attemated predictive interval   |  |                    |             |
| Sorti 2016   0.87 (0.57, 1.31)   40.50     therage 2017   0.70 (0.36, 1.35)   16.33     0.90 (0.60, 1.35)   0.81 (0.35)   43.17     subtolal ( $I^2$ = 0.0%, P = 0.807)   0.85 (0.85, 1.11)   100.00     ath estimated predictive interval   - (0.15, 4.73)   2.39     Nama 2017   0.05 (0.02, 0.15)   18.46     Sorti 2016   0.90 (0.60, 1.37)   22.39     Opage 2017   0.90 (0.60, 1.37)   22.39     Sorti 2016   0.90 (0.60, 0.137)   22.39     Opage 2017   0.39 (0.16, 0.97)   19.53     Sorti 2016   0.99 (0.60, 1.37)   22.39     Opage 2017   0.39 (0.16, 0.97)   19.53     Sorti 2016   0.99 (0.60, 1.37)   22.39     Sorti 2016   0.99 (0.60, 0.39)   0.88     Sorti 2016   0.19 (0.09, 0.69)   100.00     Ath estimated predictive interval   - (0.01, 10.54)   31.22     Sorti 2016   0.41 (0.20, 0.84)   00.00     Sorti 2016   0.41 (0.20, 0.84)   100.00     Sorti 2016   0.41 (0.20, 0.84)   100.00     Sorti 2016   0.41 (0.20, 0.84)   100.0   |  |                    |             |
| Sorti 2016   0.87 (0.57, 1.31)   40.50     therage 2017   0.70 (0.36, 1.35)   16.33     0.90 (0.60, 1.35)   0.81 (0.35)   43.17     subtolal ( $I^2$ = 0.0%, P = 0.807)   0.85 (0.85, 1.11)   100.00     ath estimated predictive interval   - (0.15, 4.73)   2.39     Nama 2017   0.05 (0.02, 0.15)   18.46     Sorti 2016   0.90 (0.60, 1.37)   22.39     Opage 2017   0.90 (0.60, 1.37)   22.39     Sorti 2016   0.90 (0.60, 0.137)   22.39     Opage 2017   0.39 (0.16, 0.97)   19.53     Sorti 2016   0.99 (0.60, 1.37)   22.39     Sorti 2016   0.90 (0.60, 0.137)   22.39     Sorti 2016   0.90 (0.60, 0.97)   19.53     Sorti 2016   0.90 (0.60, 0.97)   19.53     Sorti 2016   0.90 (0.60, 0.97)   19.53     Sorti 2016   0.45 (0.27, 0.75)   35.85     Sorti 2016   0.45 (0.27, 0.75)   35.85     Sorti 2016   0.79 (0.39, 1.60)   31.03     Sorti 2016   0.79 (0.39, 1.60)   31.03     Sorti 2016   0.41 (0.20, 0.84)   100.00  <   | Fatigue  |                    |             |
| iherigar 2017   0.70 (0.36, 1.35)   16.33     fermehren 2016   0.90 (0.60, 1.35)   43.17     babtotal (P <sup>2</sup> = 0.0%, P = 0.807)   0.85 (0.65, 1.11)   100.00     ith estimated predictive interval   . (0.15, 4.73)   .     Anemia   . (0.15, 4.73)   .     tsukaw 2017   0.05 (0.02, 0.15)   18.46     Oxoni 2016   0.90 (0.60, 1.37)   22.39     Omata 2014   0.23 (0.08, 0.63)   18.73     bherigar 2017   0.39 (0.16, 0.97)   19.53     babtotal (P <sup>2</sup> = 88.3%, P = 0.000)   . (0.01, 1.0.38)   18.73     babtotal (P <sup>2</sup> = 88.3%, P = 0.000)   . (0.01, 1.0.38)   33.12     orgawa 2016   . (0.01, 10.38)   33.12     babtotal (P <sup>2</sup> = 75.7%, P = 0.016)   . (0.01, 10.38)   33.12     babtotal (P <sup>2</sup> = 75.7%, P = 0.016)   . (0.00, 1757.90)   10.000  | Conti 2016   | 0.87 (0.57, 1.31)  | 40.50       |
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| ith estimated predictive interval   . (0.15, 4.73)     Anemia   . (0.15, 4.73)     usukawa 2017   0.05 (0.02, 0.15)   18.46     0.90 (0.60, 1.37)   22.39     0.90 (0.60, 1.37)   22.39     0.91 (0.09, 0.39)   20.88     0.23 (0.08, 0.63)   18.73     0.39 (0.16, 0.97)   19.53     ubtotal ( $l^2$ = 8.3%, P = 0.000)   . (0.01, 10.54)     ith estimated predictive interval   . (0.01, 10.54)     RIbarlin dose reduction   . (0.01, 10.54)     scotta 2016   0.45 (0.27, 0.75)   35.85     (armehren 2016   0.21 (0.11, 0.38)   33.12     (armehren 2016   0.79 (0.39, 1.60)   31.03     ubtotal ( $l^2$ = 7.5, %, P = 0.016)   0.41 (0.20, 0.84)   100.00     ust ender predictive interval   . (0.01, 175.90)   31.03  |  |                    | 100.00      |
| tsukawa 2017   0.05 (0.02, 0.15)   18.46     2onti 2016   0.90 (0.60, 1.37)   22.39     0/mata 2014   0.23 (0.08, 0.63)   18.73     0.05 (0.02, 0.15)   18.46   0.90 (0.60, 1.37)   22.39     0/mata 2014   0.23 (0.08, 0.63)   18.73     0.19 (0.09, 0.39)   0.23 (0.08, 0.63)   18.73     0.19 (0.09, 0.59)   10.000   0.25 (0.09, 0.69)   100.00     it estimated predictive interval   . (0.01, 10.54)   .   .     Ribavirin dose reduction   . (0.01, 10.54)   .   .   .     conti 2016   0.45 (0.27, 0.75)   35.85   .   .   .   .     conti 2016   0.21 (0.11, 0.38)   33.12   .<   |  |                    |             |
| tsukawa 2017   0.05 (0.02, 0.15)   18.46     2onti 2016   0.90 (0.60, 1.37)   22.39     0/mata 2014   0.23 (0.08, 0.63)   18.73     0.05 (0.02, 0.15)   18.46   0.90 (0.60, 1.37)   22.39     0/mata 2014   0.23 (0.08, 0.63)   18.73     0.19 (0.09, 0.39)   0.23 (0.08, 0.63)   18.73     0.19 (0.09, 0.59)   10.000   0.25 (0.09, 0.69)   100.00     it estimated predictive interval   . (0.01, 10.54)   .   .     Ribavirin dose reduction   . (0.01, 10.54)   .   .   .     conti 2016   0.45 (0.27, 0.75)   35.85   .   .   .   .     conti 2016   0.21 (0.11, 0.38)   33.12   .<   | Anemia   |                    |             |
| bondi 2016   0.90 (0.60, 1.37)   22.39     bygawa 2016   0.19 (0.09, 0.39)   20.88     0.23 (0.08, 0.63)   18.73     0.39 (0.16, 0.97)   19.53     ubtoltal ( $l^2$ = 88.3%, P = 0.000)   0.25 (0.09, 0.69)   100.00     ith estimated predictive interval   . (0.01, 10.54)   .     Ribavirin dose reduction   0.45 (0.27, 0.75)   35.85     optia 2016   0.21 (0.11, 0.38)   33.12     (ermehren 2016   0.79 (0.39, 1.60)   31.03     ubtoltal ( $l^2$ = 75.7%, P = 0.016)   0.41 (0.20, 0.84)   100.00     it estimated predictive interval   . (0.00, 1757.90)   .   |  | 0.05 (0.02, 0.15)  | 18.46       |
| Dgawa 2016   0.19 (0.09, 0.39)   20.88     Dmata 2014   0.23 (0.08, 0.63)   18.73     0.39 (0.16, 0.97)   19.53   0.25 (0.09, 0.69)   100.00     ith estimated predictive interval   0.25 (0.09, 0.69)   100.00     Ribavirin dose reduction   . (0.01, 10.54)   .     Scott 2016   0.45 (0.27, 0.75)   35.85     Ogawa 2016   0.21 (0.11, 0.38)   33.12     fermehren 2016   0.79 (0.39, 1.60)   31.03     Subtotal (l <sup>2</sup> = 75.7%, P = 0.016)   0.41 (0.20, 0.84)   100.00     it estimated predictive interval   . (0.00, 1757.90)   100.00  | *  |                    |             |
| Data 2014   0.23 (0.08, 0.63)   18.73     sherigar 2017   0.39 (0.16, 0.97)   19.53     Subtotal (l <sup>2</sup> = 88.3%, P = 0.000)   0.25 (0.09, 0.69)   100.00     ith estimated predictive interval   .   (0.01, 10.54)     Ribavirin dose reduction   .   0.21 (0.11, 0.38)   33.12     Ogawa 2016   0.45 (0.27, 0.75)   35.85     Ogawa 2016   0.27 (0.08, 1.60)   31.03     Valuational (l <sup>2</sup> = 75.7%, P = 0.016)   0.41 (0.20, 0.84)   100.00     interval   .   (0.00, 1757.90)   100.00  |  |                    |             |
| sherigar 2017   0.39 (0.16, 0.97)   19.53     subtotal (l <sup>2</sup> = 88.3%, P = 0.000)   0.25 (0.09, 0.69)   100.00     ith estimated predictive interval   . (0.01, 10.54)   .     Ribaviri dose reduction   0.45 (0.27, 0.75)   35.85     ogawa 2016   0.21 (0.11, 0.38)   33.12     fermehren 2016   0.79 (0.39, 1.60)   31.03     subtotal (l <sup>2</sup> = 75.7%, P = 0.016)   0.41 (0.20, 0.84)   100.00     it estimated predictive interval   . (0.00, 1757.90)   .   |  |                    |             |
| Subtotal (l <sup>2</sup> = 88.3%, P = 0.00)   0.25 (0.09, 0.69)   100.00     ith estimated predictive interval   . (0.01, 10.54)   .     Ribaviri dose reduction   0.45 (0.27, 0.75)   35.85     Ogawa 2016   0.21 (0.11, 0.38)   33.12     formehren 2016   0.79 (0.39, 1.60)   31.03     Subtotal (l <sup>2</sup> = 75.7%, P = 0.016)   0.41 (0.20, 0.84)   100.00     ith estimated predictive interval   . (0.00, 1757.90)   .   |  |                    |             |
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| boni 2016   0.45 (0.27, 0.75)   35.85     bgawa 2016   0.21 (0.11, 0.38)   33.12     fermehren 2016   0.79 (0.39, 1.60)   31.03     bjubtotal (l <sup>2</sup> = 75.7%, P = 0.016)   0.41 (0.20, 0.84)   100.00     ith estimated predictive interval   . (0.00, 1757.90)   | ith estimated predictive interval                  |                    | .00.00      |
| boni 2016   0.45 (0.27, 0.75)   35.85     bgawa 2016   0.21 (0.11, 0.38)   33.12     fermehren 2016   0.79 (0.39, 1.60)   31.03     bjubtotal (l <sup>2</sup> = 75.7%, P = 0.016)   0.41 (0.20, 0.84)   100.00     ith estimated predictive interval   . (0.00, 1757.90)   | Pibavirin doce reduction                           |                    |             |
| Ogawa 2016     0.21 (0.11, 0.38)     33.12       /ermehren 2016     0.79 (0.39, 1.60)     31.03       /ubtotal (l <sup>2</sup> = 75.7%, P = 0.016)     0.41 (0.20, 0.84)     100.00       /ith estimated predictive interval     . (0.00, 1757.90)     .   |  | 0.15 (0.07, 0.75)  | 05.05       |
| fermehren 2016     0.79 (0.39, 1.60)     31.03       subtotal (l <sup>2</sup> = 75.7%, P = 0.016)     0.41 (0.20, 0.84)     100.00       ith estimated predictive interval     . (0.00, 1757.90)     .   |  |                    |             |
| Subtotal (l <sup>2</sup> = 75.7%, P = 0.016)     0.41 (0.20, 0.84)     100.00       vith estimated predictive interval     . (0.00, 1757.90)   |  |                    |             |
| hith estimated predictive interval . (0.00, 1757.90)   |  |                    |             |
|  |  |                    | 100.00      |
| IOTE: Waights are from random effects analysis   | with estimated predictive interval                 | . (0.00, 1757.90)  |             |
|  | IOTE: Weights are from random effects analysis     |                    |             |

FIGURE 2 DAA safety in older people compared to younger adults. Forest plot for OR and corresponding 95% confidence intervals (CIs)

adults and older patients, respectively (OR 0.76 95%CI 0.17-2.3.5; P = 0.60).<sup>10,13,23,24,29</sup>

Prevalence of fatigue was investigated in the older population by three retrospective cohort studies which included a total of 491 patients. The symptom was very common and was reported in 27.3% and 27.9% of older and adult patients, respectively (OR 0.85 95%CI 0.65-1.11; P = 0.24).<sup>13,23,29</sup>

Age-related prevalence of hyperbilirubinemia was reported only in one study with a similar crude rate of 5.3% in both adults and older people.<sup>23</sup>

# 4 | DISCUSSION

People aged 65 years and over are estimated to be about 900 million worldwide. This percentage is expected to increase in the next few years. The prevalence of chronic hepatitis C is up to 40% in the older population.<sup>45</sup>

Due to multi-morbidity and polypharmacy, most clinical trials on DAAs have included a very limited proportion of patients older than 65 years.

However, considering the multiple beneficial effects of DAA treatment, antiviral therapy is commonly prescribed in older patients and age has never been considered a contraindication.

It has been recently shown that DAAs improve metabolic balance in CHC patients by exerting beneficial effects on fasting glucose, glycated haemoglobin and hypertension.<sup>46-50</sup>

These changes may result in a large number of benefits even in older ages such as reduction of polypharmacotherapy and cardio-vascular risk<sup>46</sup> and finally in improvement of quality of life.

Our study shows that DAA treatment of older chronic HCV patients is highly effective with a success rate that was not different from adults.

The overall analysis of 13 RCT studies did not show any significant difference in virological response in people  $\geq$  65 years as compared to adults. Antiviral regimens, treatment duration, liver cirrhosis and use of ribavirin did not impact SVR rate in older people.

The meta-analysis of SATs and observational studies, considered separately, produced the same results.

As expected, the overall SVR rate in the observational studies was lower as compared to that reported in RCTs (90.1% vs 96.9%) but no difference was observed between older and adult patients.

It could be very interesting to verify the impact of liver cirrhosis on the antiviral response to DAAs but, unfortunately, only one RCT<sup>38</sup> and three observational studies<sup>23-25</sup> included such data. The analysis of these studies demonstrates that cirrhosis does not influence SVR rate in older patients; however, the power of statistics is not strong enough to be conclusive.

In nine observational studies and in one SAT, data on SVR of patients older than 75 or 80 years were provided. The overall SVR rate was 95.5% but no difference in OR was observed. These data suggest that older adults over age 75 or 80 may be effectively treated. However, 7 out of 9 studies (632 of 773 patients) included only Japanese patients.

One of the most important reasons that has limited the antiviral treatment in the older population has been the risk of drug-drug interaction and side effects.

Taken all together, our analysis shows that anaemia is the side effect more commonly occurring in the elderly (22.7% of older treated patients) but all cases were observed in patients treated with a DAA regimen that included ribavirin. On the contrary, the risk of developing anaemia in the older group was comparable to adults in DAA regimens without ribavirin.

Such data indicate that ribavirin should be avoided in the treatment of CHC patients older than 65 years and that DAAs are safe in such a population as well as in older patients over the age of 75 if ribavirin is not included in the therapy regimen.

Our meta-analysis has several strengths. It is the first analysis of studies involving the older population treated with DAAs; the analysis included a total of 37 studies with RCTs separately analysed from observational and SATs. Moreover, a subgroup analysis of older adults over the age of 75 and 80 has been included.

Limitations of our analysis were the small number of studies included in the safety outcomes, the retrospective design of metaanalysis of observational studies and the small number of patients included in meta-analysis of RCTs.

Beyond these limitations, our data demonstrate that geriatric patients, who are generally considered a difficult-to-treat population, can be safely treated with DAAs with the same efficacy as reported in adults.

## CONFLICT OF INTEREST

The authors have no conflict of interest.

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#### SUPPORTING INFORMATION

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

How to cite this article: Villani R, Monami M, Di Cosimo F, et al. Direct-acting antivirals for HCV treatment in older patients: A systematic review and meta-analysis. *J Viral Hepat*. 2019;00:1–8. https://doi.org/10.1111/jvh.13169