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Meta-analysis: Influence of host and viral factors in patients with chronic hepatitis C genotype 4 treated with pegylated interferon and ribavirin

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Abstract

Background—The burden of hepatitis C virus genotype 4 (HCV-4) is high in Africa and East Mediterranean countries. Previous reports estimate sustained virologic response (SVR) rates in HCV-4 to be ~20–70%. However, many of these studies are limited by different study designs and small sample sizes.

Aim—Our aim was to evaluate treatment outcome and host/viral factors on SVR in HCV-4 patients treated with pegylated interferon and ribavirin (PEG IFN+RBV) in a systematic and quantitative fashion.

Methods—A comprehensive literature search in MEDLINE and EMBASE for ‘genotype 4’ was conducted in November 2013. Abstracts from AASLD, APASL, DDW, and EASL in 2012/2013

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Conflicts of Interest

Brittany E. Yee, Nghia H. Nguyen, Bing Zhang, Philip Vutien, Carrie R. Wong, and Glen A. Lutchman: None declared. Mindie H. Nguyen has served as a consultant and an advisory board member for Gilead Sciences Inc, Bristol-Myers Squibb, Novartis, and Bayer.

Authorship Statement

Guarantor of article: Dr. Mindie Nguyen

Brittany Yee: study design, data collection, data analysis and interpretation, drafting of the manuscript.

Nghia Nguyen: study design, data analysis and interpretation and participating in the drafting of the manuscript.

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Mindie Nguyen: concept development, study design, data collection, data analysis and interpretation, and critical revision of the manuscript.

All authors identified above have critically reviewed the paper and approve the final version of this paper, including the authorship statement

were reviewed. Inclusion criteria were original studies with 25 treatment-naïve HCV-4 patients treated with PEG IFN+RBV. Exclusion criteria were co-infection with HIV, HBV, or other genotypes. Effect sizes were calculated using random-effects models. Heterogeneity was determined by Cochrane Q-test (p -value <0.05) and I-squared statistic ($>50\%$).

Results—We included 51 studies (11,102 HCV-4 patients) in the primary analysis. Pooled SVR was 53% (95% CI: 50–55%) (Q-statistic = 269.20, $p < 0.05$; $I^2 = 81.43$). On sub-group analyses, SVR was significantly associated with lower viral load, OR 3.05 (CI 1.80–5.17, $p < 0.001$); mild fibrosis, OR 3.17 (CI 2.19–4.59, $p < 0.001$); and favorable IL28B polymorphisms, rs12979860 CC versus CT/TT, OR 4.70 (CI 2.87–7.69, $p < 0.001$), and rs8099917 TT versus GT/GG, OR 5.21 (CI 2.31–11.73, $p < 0.001$).

Conclusions—HCV-4 patients treated with PEG IFN+RBV may expect SVR rate of ~50%. Lower viral load, mild fibrosis, and favorable IL28B (rs12979860 CC and rs8099917 TT) are positively associated with SVR.

Keywords

sustained virologic response; pegylated interferon and ribavirin; hepatitis C; genotype 4

BACKGROUND

Hepatitis C virus (HCV) is one of the leading causes of cirrhosis and hepatocellular carcinoma worldwide, chronically infecting an estimated 170 million people globally[1–3]. In certain areas of the world, the World Health Organization estimates a high burden of HCV, especially in countries within Africa and the Eastern Mediterranean basin (highest prevalence in Egypt at 18%)[1, 3]. Approximately 21.3 million people living in Eastern Mediterranean countries are infected with HCV, which is comparable to the combined estimate of HCV carriers in the Americas and Europe[4, 5]. It is also in this region that HCV genotype 4 (HCV-4) is prevalent. In fact, HCV-4 comprises up to 80% of the HCV disease burden in many parts of the Middle East and Africa[3, 6].

While pivotal trials with interferon-based therapies have demonstrated a high treatment response rate, defined as sustained virologic response (SVR; undetectable HCV RNA 24 weeks after end-of-therapy), in patients with HCV genotypes 2 and 3, this has not been the experience in patients with HCV-4[7–9]. Treatment response in HCV-4 has been comparable to that observed in HCV genotype 1 (~40–50%).

Although previous studies have reported treatment data in HCV-4 patients treated with pegylated interferon and ribavirin (PEG IFN+RBV) to be comparable to those with HCV-1, the results suggest a wide range of SVR rates, 28–71%[8–17]. Additionally, a majority of these studies have heterogeneous study designs and different patient populations, making it difficult to draw conclusions[8–18]. Furthermore, the association between SVR and host and viral factors in HCV-4 patients during treatment is unclear given conflicting results from published studies.

Very recently, triple therapy with PEG IFN+RBV and sofosbuvir has been approved by the Food and Drug Administration in the U.S. for the treatment of HCV-4[19]. In Egypt where

the prevalence of HCV is the highest in the world and genotype 4 is predominant, the government price of sofosbuvir (Sovaldi®, Gilead Sciences, Foster City, CA, USA) has been negotiated to 900 U.S. dollars for a complete 12-week course of treatment [20]. In conjunction with decreased costs of monitoring with a 12-week regimen instead of 48-weeks, triple therapy has the potential to improve access and cure rates for people with HCV. However, this treatment option may remain elusive to patients in developing countries where the HCV-4 burden is high and funding for medications remains limited. Thus, PEG IFN+RBV may continue to be a mainstay of treatment.

Therefore, our aims are to systematically and quantitatively evaluate treatment outcome data and the influence of host and viral factors on virologic response in HCV-4 patients treated with PEG IFN+RBV.

METHODS

Data Sources and Searches

We performed a comprehensive literature search in MEDLINE and EMBASE in November 2013 with the following search term: ('genotype 4'). Studies with non-English languages were included. We also conducted a manual search of abstracts using the term 'genotype 4' from annual international scientific meetings held between 2012 and 2013 by the American Association for the Study of Liver Diseases (AASLD), Digestive Disease Week (DDW), Asian Pacific Study of the Liver (APASL), and European Association for the Study of the Liver (EASL). Additionally, we manually reviewed the bibliographies of published studies for relevant articles for inclusion into our study.

Study Selection

We considered studies for inclusion based on the following characteristics: i) original studies ii) inclusion of treatment-naïve patients iii) minimum sample size of 25 HCV-4 patients iv) treatment with PEG IFN+RBV. We excluded studies if study cohorts included patients with: hepatitis B, hepatitis D, or human immunodeficiency virus co-infection or those with other concurrent liver diseases. Two of the authors (B. Yee and B. Zhang) independently reviewed the articles, and discrepancies were reviewed by another author (M. Nguyen) and resolved by consensus.

Data Extraction

We designed a data abstraction form to collect data with the following information obtained from each study: study design, study type (randomized controlled trial (RCTs) versus observational), intention-to-treat (ITT) analysis, country of origin, practice setting, collaboration, and baseline patient characteristics inclusive of ethnicity, age, gender, ALT, fibrosis, and HCV RNA levels. Information on treatment characteristics was also collected: duration of treatment (48 versus 24 weeks), IL28B gene polymorphisms, and presence and level of liver fibrosis/cirrhosis.

Statistical Analysis

We performed statistical analyses to produce pooled event rates (overall SVR rate) with corresponding 95% confidence intervals (CIs) using random-effects (DerSimonian and Laird method) model and inverse variance method[21]. We assessed for study heterogeneity with χ^2 -based Cochrane Q-statistic with $p = 0.05$ and $I^2 = 50\%$ in adherence to the standards of quality for reporting meta-analysis from the Cochrane handbook[21]. We produced odds ratios (OR) and corresponding 95% CIs for sub-group analyses. Univariate and multivariate random-effects meta-regression on study-level characteristics was also performed to explain any observed heterogeneity in our primary outcome, as well as identify any patient-level factors that may be associated with our primary outcome[21–23]. We assessed for potential publication bias graphically with a funnel plot of $\ln[OR]$ against its standard error (SE). Influence analysis with one-study removal method to identify potential outliers contributing to our pooled estimate was conducted where appropriate. The graphs for funnel plots, with accompanying Egger's test, and influence analyses may be found in the supplemental pages. In studies with zero-cell counts, a fixed value of '0.5' was added to all cells of study results tables[21]. All statistical tests were two-sided. All calculations were performed using Comprehensive Meta-Analysis, version 2 (Biostat, Englewood, New Jersey, USA), and STATA 11 (StataCorporation, College Station, Texas)[22, 24, 25].

RESULTS

Literature Search Results

Our literature search identified 1,798 studies (729 articles from MEDLINE and 1,069 articles from EMBASE) and 14,648 abstracts from major liver society meetings held in 2012 and 2013. Eighty-four studies were closely evaluated for eligibility[10–16, 18, 26–101]. Fourteen studies did not have extractable treatment outcomes data[26, 29, 36, 47, 50, 58, 61, 64, 74, 86, 87, 92, 100, 101]. Six were redundant[49, 51, 57, 68, 89, 99] and four were not relevant[30, 43, 60, 94]. Two studies did not contain original data[52, 98]. Three studies did not evaluate treatment-naïve patients[31, 32, 97], one study did not have at least 25 HCV-4 patients[33], and three studies included patients co-infected with hepatitis B virus, HIV, or other liver diseases[44, 70, 82]. After conducting a comprehensive review, a total of 44 articles and 7 abstracts met eligibility criteria and were included in the meta-analysis (Figure 1).

Study Characteristics

There were 51 studies with a total of 11,102 HCV-4 patients included in the primary analysis (Table 1)[10–16, 18, 27, 28, 34, 35, 37–42, 45, 46, 48, 53–56, 59, 62, 63, 65–67, 69, 71–73, 75–81, 83–85, 88, 90, 91, 93, 95, 96]. The majority of studies (40/51, 78%) originated from the Middle East[10–13, 15, 16, 18, 27, 28, 34, 35, 37, 40–42, 45, 46, 53–56, 59, 62, 63, 66, 67, 69, 72, 75, 78, 80, 81, 83–85, 88, 91, 95] and Europe (9/51, 18%)[14, 38, 39, 65, 71, 76, 79, 93, 96]. One originated in Cameroon[77] and one multi-center study was conducted in 19 countries[73]. Most studies were performed in a university setting and had an ITT analysis. In all studies, the majority of patients were male. Mean age ranged from 38.2 to 57.1 years. All but one study included SVR in patients treated for 48 weeks[71].

SVR Rates Overall and by Study Design

Overall—In 51 studies with a total of 11,102 HCV-4 patients, the pooled SVR rate was 53% (CI: 50–55%) (Q-statistic = 269.20, $p < 0.05$; $I^2 = 81.43$) (Figure 2). Funnel plot and Egger's test showed no significant publication bias ($p = 0.39$) (Supplement Figure 1a). On influence analysis, our pooled event rate varied by no more than ~1%, demonstrating the robustness of our estimate (Supplement Figure 1b).

RCT versus non-RCT Studies—When comparing RCTs versus non-RCT studies, we observed a pooled SVR rate of 60% (CI: 53–68%) in the six RCTs[10, 13, 16, 18, 54, 93] compared to 52% (CI: 49–55%) in 45 non-RCTs[11, 12, 14, 15, 27, 28, 34, 35, 37–42, 45, 46, 48, 53, 55, 56, 59, 62, 63, 65–67, 69, 71–73, 75–81, 83–85, 88, 90, 91, 95, 96] (Figure 3). This finding was statistically significant with $p = 0.043$. Heterogeneity was observed in both sub-groups ($I^2 = 82.40$ for non-RCT studies; $I^2 = 48.72$ for RCTs).

Prospective versus Retrospective Studies—Sub-group-analysis by prospective and retrospective studies showed similar SVR rates: 53% (CI: 50–56%) in forty-three prospective studies[10, 11, 13–16, 18, 27, 28, 34, 38–42, 46, 48, 53–56, 62, 63, 65–67, 69, 72, 73, 75–78, 80, 81, 83, 84, 88, 90, 91, 93, 95, 96] and 53% (CI: 46–59%) in eight retrospective studies[12, 35, 37, 45, 59, 71, 79, 85]. Significant heterogeneity was observed in both sub-group analyses with $I^2 > 50\%$ (Figure 4).

Random-effects Meta-regression of Study Characteristics—Study characteristics of all 51 studies were explored on univariate and multivariate random-effects meta-regression to explain the heterogeneity observed in our primary outcome and also quantify any residual heterogeneity. On univariate and multivariate analyses, no study characteristics were found to be significant predictors of heterogeneity in our pooled SVR rate (Table 2).

SVR Rates by Host and Viral Factors

Lower versus Higher Viral Load—Eleven studies with a total of 1,130 patients [539 (48%) with lower viral load and 591 (52%) with higher viral load] had treatment outcomes directly comparing lower versus higher baseline viral load (Supplement Figure 2a)[11, 34, 54, 56, 62, 63, 67, 69, 76–78].

SVR estimate was 67% (CI: 62–72%) in patients with lower viral load and 45% (CI: 35–54%) in patients with higher viral load. Although the definition of higher viral load varied across studies, ranging from a threshold of $>200,000$ IU/ml to $>800,000$ IU/ml, we observed a pooled OR of 3.05 (CI: 1.80–5.17, $p < 0.001$) favoring patients with lower baseline viral load. Significant heterogeneity was observed in our model (Q-statistic = 28.70, $p < 0.05$; $I^2 = 65.16$) (Supplement Figure 2b and Supplement Figure 2c).

Mild versus Advanced/Severe Hepatic Fibrosis—There were fourteen studies with a total of 3,116 patients [1580 (51%) mild fibrosis and 1,536 (49%) severe fibrosis] that evaluated the influence of fibrosis on treatment response. Eleven studies used the METAVIR scoring system[11, 62, 63, 66, 67, 69, 76, 77, 79, 80, 95], while three other

studies used a different scoring system (Knodel, Ishak, or Scheuer) to classify patients as having either mild or severe fibrosis[42, 56, 78].

Overall, SVR was 66% (CI: 60–72%) for patients with mild fibrosis and 39% (CI: 35–43%) for those with severe fibrosis. Compared to patients with severe fibrosis, patients with mild fibrosis were significantly more likely to obtain SVR, 3.17 (CI: 2.19–4.59, $p < 0.001$) (Q-statistic = 39.45, $P < 0.05$, $I^2 = 67.05$) (Supplement Figure 3a, Supplement Figure 3b, Supplement Figure 3c).

In the eleven studies that evaluated levels of fibrosis with METAVIR scoring system[102], there were a total of 3,116 patients [1580 (51%) with mild fibrosis and 1536 (49%) with severe fibrosis] (Supplement Figure 4a)[17, 62, 63, 66, 67, 69, 76, 77, 79, 80, 95]. In this sub-group analysis, SVR in mild versus severe fibrosis was 65% (CI: 57–71%) and 38% (CI: 34–42%), respectively. In a direct comparison, patients with mild fibrosis were more likely to achieve SVR, OR 3.00 (CI: 1.98–4.56) (Q-statistic = 27.96, $p < 0.05$, $I^2 = 64.23$). In all but one study, mild fibrosis and severe fibrosis was defined as F0-F2 and F3-F4, respectively – the study by Khairy M *et al* defined mild fibrosis as F0-F1 and severe fibrosis as F2-F4[66]. On one study removed influence analysis, our pooled OR increased by 12%, from 3.003 to 3.374, showing a stronger association between mild fibrosis and SVR with omission of the study by Khairy M *et al*[66] (Supplement Figure 4b, Supplement Figure 4c). By including patients with METAVIR score of F2 into the severe fibrotic group, this study may have diminished the effect size between mild and severe fibrosis.

IL 28B CC versus CT/TT Polymorphism—Nine studies with a total of 1,893 patients [572 (30%) CC and 1321 (70%) CT/TT] assessed SVR in rs12979860 CC versus CT/TT (Figure 6a)[27, 37–39, 41, 42, 80, 81, 88].

SVR rate in CC patients was 75% (CI: 68–82%) and SVR in CT/TT patients was 40% (CI: 35–46%). The OR relating SVR with IL28B polymorphism was 4.70 (95% CI: 2.87–7.69, $p < 0.001$), significantly favoring patients with rs12979860 CC phenotype. Significant heterogeneity was observed in both our sub-group analyses (Q-statistic = 28.89, $p < 0.05$, $I^2 = 72.31$).

IL 28B TT versus GT/GG Polymorphism—Five studies with a total of 751 HCV-4 patients [406 (54%) TT and 345 (46%) GT/GG] assessed SVR in rs8099917 TT compared to GT/GG (Figure 6b)[27, 37, 42, 81, 88].

SVR rates were 69% (CI: 59–77%) in TT and 33% (CI: 21–48%) in GT/GG patients. The OR of SVR was 5.21 (CI: 2.31–11.73, $p < 0.001$) in favor of patients with rs8099917 TT. Significant heterogeneity was observed in our model (Q-statistic = 17.85, $p < 0.05$, $I^2 = 77.59$).

Male versus Female Patients—Twenty-three studies with total of 3,211 HCV-4 patients [2,322 (72%) males and 889 (28%) females] included information on the influence of gender on SVR.

SVR in males was 54% (CI: 49–58%) and SVR in females was 54% (CI: 49–60%). We did not observe a significant difference in SVR between males and females with an OR of 0.98 (CI 0.76–1.27, $p=0.87$) (Supplement Figure 5a, Supplement Figure 5b, Supplement Figure 5c). Significant heterogeneity was observed in our model (Q -statistic = 41.82, $P<0.05$; $I^2 = 47.39$).

Treatment Duration: 24 versus 48 weeks—Two studies with a total of 278 patients [140 (50%) treated for 48-weeks and 138 (50%) treated for 24-weeks] compared treatment response in patients treated for 48 weeks versus 24 weeks of PEG IFN+RBV (16, 24).

SVR was 70% (CI: 62–77%) and 49% (CI: 15–84%) in patients treated for 48 weeks and 24 weeks, respectively. However, the difference in treatment response between these two groups did not reach statistical significance, OR 2.57 (CI: 0.58–11.34, $p=0.21$) (Supplement Figure 6).

Random-effects Meta-regression of Age and Baseline ALT level—Although we did not have individual level data available for sub-group analyses of age and baseline ALT levels, there were summary statistics available (mean averages) for a random-effects meta-regression.

On univariate analysis of 38 studies that included mean age, we detected a trend for studies with older mean ages to be associated with lower SVR rates, $\beta=-0.04$ (CI: -0.07 – 0.0002 , $p=0.05$; I^2 residual = 79.1%; Adjusted $R^2 = 11.3\%$) (Figure 5). On a multivariate meta-regression analysis inclusive of mean age and proportion of patients with advanced fibrosis (as defined by each study), there was no association between age and SVR ($\beta= -0.002$, $p=0.91$). The negative association between increasing age and SVR we observed on univariate meta-regression could be explained by the fact that older patients tend to have more fibrosis than younger patients.

On univariate analysis of 27 studies with mean baseline ALT levels, we observed a trend for studies with higher mean baseline ALT levels to have a positive association with higher SVR rates, $\beta=0.004$ (CI: -0.0007 – 0.01 , $p=0.09$; I^2 residual = 78.1%; Adjusted $R^2 = 17.38\%$) (Supplement Figure 7).

Publication Bias

In all our sub-group analyses, we did not observe any publication bias (no significant asymmetry on funnel plot and accompanying Egger's tests with $p>0.05$) (Supplement Figure 1a, Supplement Figure 2b, Supplement Figure 3b, Supplement Figure 4b, Supplement Figure 5b).

DISCUSSION

In our current meta-analysis, which included 51 studies with a total of 11,102 HCV-4 patients treated with PEG IFN+RBV, we observed a pooled SVR rate of 53% (CI: 50–55%). This estimate remained robust on influence analysis and no publication bias was observed. In sub-group analyses by study characteristics, pooled SVR rates were the same in

retrospective and prospective studies while there was a significantly lower pooled SVR rate in non-RCTs compared with RCTs: 52% (CI: 49–55%) versus 60% (CI: 53–68%), respectively ($p = 0.043$). However, on multivariate random-effects meta-regression inclusive of study nature (retrospective vs prospective), country of origin (European vs Eastern Mediterranean basin), and ITT vs non-ITT analysis, we did not find the same significant association between SVR rate and study design (non-RCTs versus RCTs, $p = 0.16$). Since a random-effect meta-regression is a more conservative approach for exploring observed and residual heterogeneity in a pooled estimate, the difference in SVR rates between non-RCTs and RCTs in our sub-group analysis was most likely confounded by the underlying differences in our included study populations.

Currently, there are two published meta-analyses on HCV-4 patients treated with PEG IFN +RBV that evaluated pooled treatment data[6, 23]. In their studies, Aljumah AA *et al* and Khuroo MS *et al* observed pooled SVR rates of 51% and 55%, respectively, which was similar to our finding (53%). However, both studies were limited by small sample sizes; included only five[6] or six[17] RCTs only; and did not include sub-group analyses on host and viral factors on SVR. In contrast, our study included a large number of diverse studies (6 RCTs and 45 non-RCTs studies, $n = 11,102$) and also evaluated the influence of host and viral factors on SVR rates in HCV-4 patients.

Based on pivotal studies, SVR is selectively higher in patients with milder forms of fibrosis[7, 103–105]. While most of the literature note this positive link, there are some studies with negative findings[63, 66, 76, 77]. However, these negative studies often have heterogeneous study designs, small sample sizes and variable patient populations. In our sub-group analysis, we found a favorable SVR response in patients with mild versus severe fibrosis, OR 3.17 (CI 2.19–4.59, $p < 0.001$), across studies with different scoring systems, and also in studies using METAVIR system only, OR 3.00 (CI 1.98–4.56, $p < 0.001$). Our finding is consistent with previous studies that established a relationship between severe fibrosis with lower SVR rates and poorer clinical outcomes[106–110].

Another established determinant of treatment response is baseline viral load, with patients starting with a lower baseline HCV RNA having a greater likelihood of achieving SVR[7, 103, 105]. In our study, we found a similar association between lower baseline viral load and higher SVR rates than those with higher viral load, OR 3.05 (CI: 1.80–5.17, $p < 0.001$). While the threshold for higher viral load varied across studies (ranging from $>200,000$ IU/ml to $>800,000$ IU/ml), our pooled OR did not change by more than 18% on influence analysis.

In regards to *IL28B* polymorphism, based on numerous genome-wide association and human subject studies, investigators have established an important link between common polymorphisms and SVR[39, 42, 111, 112]. In our sub-group analyses, which included 1,893 HCV-4 patients with *IL28B* data, we found a favorable association between SVR and rs12979860 CC genotype versus CT/TT, OR 4.70 (CI 2.87–7.69, $p < 0.001$), and between SVR and rs8099917 TT genotype versus GT/GG, OR 5.21 (CI: 2.31–11.73, $p < 0.001$). Our findings are consistent with established studies that have shown a strong link between certain *IL28* polymorphisms and high SVR rates[39, 42, 112].

While the majority of the literature shows no difference in SVR rates between genders, a study by Kamal SM *et al* that included a total of 279 HCV-4 patients (145 (52%) males and 134 (48%) females) observed a significantly higher SVR in females versus males, OR 2.65 (CI 1.63–4.31, $p<0.001$). However, it is difficult to draw conclusions from one study among many others that have not found a positive association. On the other hand, many of these negative studies had variable study designs and included small numbers of female subjects. In our sub-group analysis, inclusive of 23 studies with direct comparison between genders, with a total of 3,211 HCV-4 patients [2,322 (72%) males and 889 (28%) females], we did not observe a significant difference in SVR rates between the two genders. The ratio of males to females likely demonstrates a male treatment bias since the frequency of HCV-4 is similar for both genders based on several epidemiological studies [113–115].

Currently, the optimal treatment duration for PEG IFN+RBV in HCV-4 patients is unclear with few published studies on this topic. In the only two studies with direct comparison between 48 and 24 weeks of treatment, the results have been conflicting. One study by El Khayat HR *et al* that included 44 patients treated for 48 weeks and 43 patients treated for 24 weeks, respectively, and found no difference in SVR rates, OR 1.16 (CI 0.46–2.93 $p=0.76$), while another study by Kamal SM *et al* that included twice as many patients in their sample size (96 patients treated for 48 weeks, 96 patients treated for 36 weeks and 95 patients treated for 24 weeks) found a significant difference in SVR rates, OR 5.26 (CI 2.84–9.76, $p<0.001$), in favor of 48 versus 24 weeks [10, 18]. Several differences may explain these findings: Kamal SM *et al* included patients with a higher viral load (mean 2.8×10^6 IU/ml in both cohorts) than patients in El Khayat *et al* (mean viral load of 144,640 IU/ml in 48-week and 135,490 IU/ml in 24-week cohorts) and patients in Kamal SM *et al* were treated with PEG IFN alpha-2b, while patients in El Khayat *et al* were treated with PEG IFN alpha-2a [16, 24]. In our sub-group analysis of these two studies, we found no significant difference in SVR rates between 48 and 24 weeks of treatment, OR 2.57 (CI 0.58–11.34, $p=0.21$). Based on the limited sample size of patients and included studies in our sub-group analysis, this analysis is an underpowered comparison and additional research is needed to define the optimal treatment duration for HCV-4 with PEG IFN+RBV.

While we did not have individual patient-level data available for age and baseline ALT levels, we were able to collect study-level summary statistics for these factors (mean averages). On univariate random-effects meta-regression, we detected a trend for studies with older mean age to be associated with lower SVR rates, $\beta=-0.04$ (CI: $-0.07-0.0002$, $p=0.05$), and a trend for studies with higher mean baseline ALT levels to be associated with higher SVR rates, $\beta=0.004$ (CI: $-0.0007-0.01$, $p=0.09$). While our data suggests associations between age and SVR rates and baseline ALT levels and SVR rates, additional studies are needed to further explore these observations since we cannot make firm conclusions based on summary statistics alone.

Although our meta-analysis included a large number of studies and patients, it is not without limitations. One limitation of our study is the heterogeneity of our data given our broad inclusion criteria, which captured many studies of different study and patient characteristics. However, we accounted for this by estimating effect sizes from random effects modeling and sub-group analyses by various study and patient characteristics. We also attempted to

explain the heterogeneity we detected by performing univariate and multivariate random-effects meta-regression, which were more conservative analyses than sub-group analyses. Furthermore, influence analyses and funnel plots with accompanying Egger's tests were performed to identify any potential bias or outliers in our data, which we did not find. We also sought to minimize any publication bias by performing a comprehensive literature review from two major databases (MEDLINE and EMBASE), a manual search of abstracts in the last two years in four major international scientific journals, and a manual search for relevant articles in the bibliographies of published studies.

In summary, our study is a comprehensive and systematic evaluation of pooled SVR data in HCV-4 patients treated with PEG IFN+RBV across multiple studies of different study designs and patient characteristics. Overall, we observed a pooled SVR rate of 53% in our patient population and found an association with SVR with mild fibrosis, lower baseline viral load, and favorable *IL28B* polymorphisms (rs12979860 CC and rs8099917 TT genotypes).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

HCV	Hepatitis C Virus
HCV-4	Hepatitis C Virus Genotype 4
HCV-1	Hepatitis C Virus Genotype 1
SVR	Sustained Virologic Response
RVR	Rapid Virologic Response
EVR	Early Virologic Response
PEG IFN+RBV	Pegylated Interferon and Ribavirin
AASLD	American Association for the Study of Liver Diseases
APASL	Asian Pacific Study of the Liver
DDW	Digestive Disease Week
EASL	European Association for the Study of the Liver
RCT	Randomized Controlled Trial
ITT	Intention-to-treat

OR

Odds Ratio

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Figure 1.

Flow diagram of articles and abstracts meeting inclusion criteria for meta-analysis

Figure 2.
Overall SVR rate in HCV genotype 4 treated with PEG IFN+RBV

Figure 3.
SVR rates in randomized controlled trials versus non-randomized controlled trials

Figure 4.
SVR rates in prospective versus retrospective studies

Figure 5.
Random effects meta-regression of age

Figure 6.

a. SVR rates in IL28B polymorphisms: rs12979860-CC vs. CT/TT

b. SVR rates in IL28B polymorphisms: rs8099917-TT vs. GT/GG

Table 1

Characteristics of studies included in meta-analysis of HCV-4 patients treated with PEG IFN+RBV

First Author, Year	Country	Study design	No. of HCV-4 pts	$b_{\text{HCV RNA}}$ level	Male (%)	b_{Age} (years)	N included in analysis
Ragheb M, 2013[81]	Egypt	Prospective	119	2.5×10^6 IU/ml	76	42.7	119
Shaker O, 2013[88]	Egypt	Prospective	100	-	60	39.48	100
Saad Y, 2013[83]	Egypt	Prospective	100	-	68	40.90	100
Ahmed M, 2013[15]	Egypt	Prospective	102	-	85	49.3	102
Mahmoud M, 2013[72]	Egypt	Prospective	80	-	88	49.0	80
Khairy M, 2013[66]	Egypt	Prospective	263	5.06 log IU/ml	72	44.1	263
Abdo A, 2013[27]	Saudi Arabia	Prospective	129	5.9 log IU/ml	51	Median 49	129
El Raziky M, 2013[12]	Egypt	Retrospective	3718	1091006.52 IU/ml	81	41.9	3718
Shahin Y, 2013[85]	Egypt	Retrospective	1081	-	-	-	1081
Omran M, 2013[78]	Egypt	Prospective	115	397492.8 IU/ml	84	40.94	115
Derbala M, 2012[41]	Qatar	Prospective	201	-	90	Median 47	201
Monis A, 2012[75]	Egypt	Prospective	38	-	95	40	38
Saad Y, 2012[84]	Egypt	Prospective	100	-	56	39.2	100
El Khayat H, 2012[10]	Egypt	Prospective	46	4.8 log IU/ml	87	42.0	46
Karatapanis S, 2011[65]	Greece	Prospective	117	-	71	43.5	117
Stauber R, 2011[93]	Austria	RCT	26	-	-	-	26
Afifi M, 2010[28]	Egypt	Prospective	102	-	-	-	102
Shiha G, 2010[91]	Egypt	Prospective	104	-	82	-	104
Esmat G, 2009[55]	Egypt	Prospective	100	-	-	-	100
Derbala M, 2013[42]	Qatar	Prospective	159	Median 449165.5 IU/ml	91	46.5	159
Al-Ashgar H, 2013[34]	Saudi Arabia	Prospective	64	-	64	38.7	64
Farag R, 2013[56]	Egypt	Prospective	200	-	81	41.64	200
Urquijo J, 2013[96]	Spain	Prospective	198	693749.5 IU/ml	80	39.31	198
Antaki N, 2012[37]	Syria	Retrospective	182	-	32	Median 52	182
Pasha H, 2013[80]	Egypt	Prospective	440	6.9 log IU/ml	66	57.1	440
al Khayat H, 2012[10]	Egypt	RCT	87	Median 144640 IU/ml	75	41.55	87

First Author, Year	Country	Study design	No. of HCV-4 pts	<i>b</i> _{HCV RNA level}	Male (%)	<i>b</i> Age (years)	N included in analysis
Shaker O, 2012[90]	Egypt	Prospective	100	-	56	38.18	100
El-Shamy A, 2012[53]	Egypt	Prospective	43	259061.63 IU/ml	77	41.54	43
Papastergiou V, 2012[79]	Greece	Retrospective	177	-	81	44.6	177
Marcellin P, 2012[73]	19 countries	Prospective	317	5.3 log IU/ml	68	44.5	317
Khattab M, 2012[69]	Egypt	Prospective	107	374924.2 IU/ml	80	41.4	107
Al-Enzi S, 2011[35]	Kuwait	Retrospective	51	-	-	-	51
Asselah T, 2012[38]	France	Prospective	82	-	77	44.3	82
Eskander E, 2012[54]	Egypt	RCT	45	-	78	38.66	45
De Nicola S, 2012[39]	Italy	Prospective	112	-	91	Median 46	103
Kamal S, 2011[16]	Egypt	RCT	217	763845.67 IU/ml	49	41.43	217
Ibrahim M, 2010[63]	Egypt	Prospective	56	-	89	Median 43	56
Derbala M, 2011[45]	Qatar	Retrospective	176	-	85	Median 46	176
Taha A, 2010[95]	Egypt	Prospective	107	535579.9 IU/ml	56	46.08	107
Khattab M, 2010[67]	Egypt	Prospective	131	-	48	41.6	131
Moucarri R, 2009[76]	France	Prospective	108	5.5 log IU/ml	79	44	108
El Mahkzangy H, 2009[11]	Egypt	Prospective	95	5.4 log IU/ml	85	42	95
Njoum R, 2008[77]	Cameroon	Prospective	35	-	71	54.3	26
<i>a</i> Lopez-Alonso G, 2008[71]	Spain	Retrospective	30	-	67	40	30
Derbala M, 2008[46]	Egypt	Prospective	84	-	88	45	84
Gad R, 2008[59]	Egypt	Retrospective	169	302 × 10 ³ IU/ml	81	41.21	169
Kamal S, 2007[13]	Egypt	RCT	50	6.0 log IU/ml	52	43.2	50
Derbala M, 2005[40]	Egypt	Prospective	30	496 × 10 ³ IU/ml	87	38.7	30
<i>a</i> Kamal S, 2005[18]	Egypt	RCT	287	2.77 × 10 ⁶ IU/ml	52	42.23	287
Hasan F, 2004[62]	Kuwait	Prospective	66	4.2 × 10 ⁶ IU/ml	73	45	66
Mauss S, 2012[14]	Germany	Prospective	474	-	76	Median 41	474

^aEl Khayat *et al* 2012 and Kamal *et al*, 2005 evaluated patients with 24-weeks versus 48-weeks of treatment while Lopez-Alonso *et al* 2008 evaluated patients with 24-weeks of treatment only. All other studies evaluated patients with 48-weeks of treatment.

^b HCV RNA and age are presented as means unless otherwise specified.

Table 2

Univariate and multivariate random-effects meta-regression on study characteristics and pooled SVR rate in 51 studies

Characteristics	Univariate Analysis		Multivariate analysis ^a	
	β (95% CI)	p-value	β (95% CI)	p-value
Non-RCTs vs RCTs	-0.09 (-0.20-0.03)	0.12	-0.29 (-0.69-0.12)	0.16
Retrospective vs Prospective	-0.01 (-0.35-0.32)	0.12	-0.05 (-0.39-0.28)	0.75
Europe vs Eastern Mediterranean Basin	-0.28 (-0.63-0.07)	0.12	-0.27 (-0.63-0.09)	0.14
ITT vs non-ITT	0.19 (-0.25-0.63)	0.38	0.20 (-0.24-0.64)	0.36

^aI-squared residual = 78.9%; Adjusted R-squared = 3.4%; $p=0.24$ for overall model

RCTs = randomized controlled trials

ITT = intention-to-treat