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Magnitude and Kinetics of Decrease in Liver Stiffness After Antiviral Therapy in Patients With Chronic Hepatitis C: A Systematic Review and Meta-analysis

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Abstract

Background & Aims—We performed a systematic review and meta-analysis to estimate the decrease in liver stiffness, measured by vibration-controlled transient elastrography (VCTE), in patients with hepatitis C virus (HCV) infection who achieved a sustained virologic response (SVR).

Methods—We searched the literature through October 2016 for observational studies or randomized controlled trials of adults with HCV infection who received antiviral therapy (either direct acting antiviral agents or interferon-based therapies), underwent liver stiffness measurement

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- Acquisition of data: SS, AF
- Analysis and interpretation of data: SS, AF, RL, YFY
- Drafting of the manuscript: SS, AF
- Critical revision of the manuscript for important intellectual content: RL, YFY
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using VCTE before starting therapy, and had at least 1 follow-up VCTE after completion of therapy; studies also provided data on mean or median liver stiffness measurements for patients who did and did not achieve an SVR. We identified 24 studies, and estimated weighted mean difference (and 95% CI) in liver stiffness in patients with vs without SVR using random-effects meta-analysis.

Results—In patients who achieved SVR, liver stiffness decreased by 2.4 kPa at the end of therapy (95% CI, −1.7 to −3.0), by 3.1 kPa 1–6 months after therapy (95% CI, −1.6 to −4.7), by 3.2 kPa 6–12 months after therapy (90% CI, −2.6 to −3.9), and 4.1 kPa 12 months or more after therapy (95% CI, −3.3 to −4.9) (median decrease, 28.2%; interquartile range, 21.8–34.8). In contrast, there was no significant change in liver stiffness in patients who did not achieve an SVR (at 6–12 months after therapy, decrease of 0.6 kPa; 95% CI, −1.7 to 0.5). Decreases in liver stiffness were significantly greater in patients treated with direct-acting antiviral agents than with interferon-based therapy (decrease of 4.5 kPa vs decrease of 2.6 kPa; P=.03), cirrhosis at baseline (decrease of 5.1k Pa vs decrease of 2.8k Pa in patients with no cirrhosis; P=.02), or high pre-treatment levels of alanine aminotransferase (P<.01). Among patients with baseline liver stiffness greater than 9.5 kPa, 47% (95% CI, 27%–68%) achieved post-treatment liver stiffness of less than 9.5kPa.

Conclusion—In a systematic review and meta-analysis, we associated eradication of HCV infection (SVR) with significant decreases in liver stiffness—particularly in patients with high baseline level of inflammation or patients who received direct-acting antiviral agents. Almost half the patients considered to have advanced fibrosis, based on VCTE, before therapy achieved post-treatment liver stiffness levels below 9.5 kPa. Clinical Trial Registration no: CRD42016051034

Keywords

DAA; ALT; cirrhosis; treatment success

INTRODUCTION

Hepatitis C virus infection (HCV) is one of the leading causes of liver cirrhosis and hepatocellular carcinoma (HCC) with approximately 170 million people infected with the virus worldwide.[1, 2] Recently, the Centers for Disease Control, and later the United States Preventive Services Task Force recommended screening all adults born between 1945–65 for HCV.[3] Fibrosis stage and/or liver stiffness are key predictors of adverse outcomes, and in recent years, liver stiffness assessment using vibration controlled transient elastography (VCTE) has superseded liver biopsy as a favored non-invasive modality.[4, 5] In fact, draft American Gastroenterological Association (AGA) guidelines recommend using VCTE to replace liver biopsy in adults with HCV.

Viral eradication (assessed as sustained virologic response [SVR] 12–24 weeks after completion of therapy) has been associated with decline in liver stiffness, due to a combination of decrease in hepatic inflammation and possible fibrosis regression, but there has been limited assessment of the magnitude of decline. With increasing numbers of patients being cured of HCV, this decline in liver stiffness may be an important consequence

of antiviral therapy, translating into favorable long-term clinically relevant outcomes, though definitive evidence in this regard is still lacking.

Hence, we conducted a systematic review of studies with paired liver stiffness measurement using VCTE, before and after antiviral therapy. We estimated (a) magnitude of change in liver stiffness at different time points after antiviral therapy in patients achieving SVR (end of treatment [EOT], 1–6m after EOT including SVR12, 6–12m after EOT including SVR24, and >12m after EOT), (b) magnitude of change in liver stiffness among those who achieve SVR and those who do not achieve SVR, to estimate net decline in liver stiffness after successful viral eradication, and (c) what proportion of patients with baseline liver stiffness >9.5 (corresponding to fibrosis stages, F3 or F4), achieve liver stiffness <9.5kPa (corresponding to <F3) 6–12 months after viral eradication.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the process followed an *a priori* established protocol, registered on PROSPERO (CRD: CRD42016051034).[6]

Selection Criteria

We included observational studies or randomized controlled trials (RCTs): (1) conducted in adults (>18y) with HCV who received antiviral therapy (with either direct acting antiviral agents [DAAs] or interferon-based therapies), (2) underwent liver stiffness measurement using VCTE before starting therapy and (3) at least one follow-up VCTE performed after completion of therapy, and (4) provided data on mean/median liver stiffness with measure of variability, stratified by patients who achieved SVR and those who didn't achieve SVR (i.e., both baseline and follow-up liver stiffness reported separately in patients who achieved SVR and those who did not).

We excluded the following studies: (1) cross-sectional studies with no post-treatment follow-up liver stiffness assessment, (2) studies conducted in untreated patients with HCV or with other etiologies of liver disease (without sufficient subgroup data on patients with HCV), (3) baseline fibrosis assessed only using liver biopsy (without liver stiffness assessment), (4) liver stiffness assessed with non-invasive tools other than VCTE, (5) data were not stratified based on SVR status, or (6) if <80% of the study cohort underwent follow-up VCTE after completion of therapy. In the case of duplicate studies from the same cohort, we included data from the most recent comprehensive report.

Search Strategy

We conducted a systematic search of multiple electronic databases (including included Medline, EMBASE, Scopus, Web of Science, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews) from January 1, 2005 to October 31, 2016, with no language restrictions. The search was designed and conducted by an experienced medical librarian with input from the study investigators, using controlled vocabulary supplemented with keywords, for observational studies and RCTs of HCV patients who underwent antiviral treatment. The details of the search strategy are included in

the online supplement. The titles and abstract of studies identified in the search were reviewed by 2 investigators independently (S.S., A.F.) to exclude studies that did not address the research question of interest, based on the aforementioned pre-specified inclusion and exclusion criteria; full text of the remaining articles was examined to determine whether it contained relevant and complete information. Additional studies were searched from the bibliographies of the selected articles and review articles on the topic. We also manually searched conference proceedings of major gastroenterology and hepatology conferences (American Association for the Study of the Liver Meeting, European Association for the Study of the Liver International Liver Congress, and Digestive Diseases Week organized in conjunction with the American Gastroenterological Association) from 2013–2016 to identify additional studies published only in abstract form. Figure 1 reports the schematic diagram of study selection. Chance-adjusted agreement between reviewers was high, but not formally calculated.

Data Abstraction and Risk of Bias Assessment

Data on the following study- and patient-related characteristics were abstracted onto a standardized form: (1) study characteristics – first author, time period of study/year of publication, country of the population studied; (2) patient characteristics – mean age, sex, body mass index (BMI), co-infection with human immunodeficiency virus (HIV) or hepatitis B virus, HCV viral genotype and viral load, baseline aspartate aminotransferase (AST) and alanine aminotransferase (ALT), baseline cirrhosis, type and duration of antiviral therapy, number of patients who achieved and did not achieve SVR; (3) liver stiffness assessment – number of patients who underwent baseline and follow-up VCTE, timing of VCTE in relation to antiviral therapy and number of patients studied at each time point, mean/median liver stiffness along with measure of variability (standard deviation [s.d.], range, or interquartile range [IQR]) both before and after therapy, stratified by SVR status.

The risk of bias in included studies was assessed using a modified scale derived from the Newcastle–Ottawa scale,[7] and included the following 6 items: (1) representative of the average adult in the community (1 point for unselected participants in population-based, multicenter studies or RCTs; 0.5 points for unselected participants in single-center hospital-based study; 0 points if non-consecutive selected group of patients), (2) large cohort size (1 point if size >200 patients; 0.5 points if size between 50 and 200 patients; 0 points if size <50 patients), (3) adequate follow-up length after antiviral therapy (1 point if mean follow-up of cohort >2 years ; 0.5 points if 6 months-2 years; 0 points if <6 months), (4) adequate reporting of conditions in which VCTE was performed both at baseline and follow-up such as fasting status or transaminase level <2× upper limit of normal (1 point if adequately described both pre- and post-antiviral therapy; 0.5 points if described only at baseline; 0 points if not mentioned), (5) presence of confounders for liver stiffness assessment (which may independently modify stiffness even after achieving SVR) such as acute hepatitis, HIV or HBV co-infection, excessive alcohol consumption (1 point if absence of all confounders; 0.5 if presence of 1 confounder in a subset of patients (<30% of cohort); 0 points if >30% of cohort has confounders or data not reported), and (6) other potential sources of risk of bias. Studies with score >4, 3–4 and <3 were suggestive of low, moderate or high risk of bias.

Outcomes assessed

Primary outcome—The primary outcome of interest was change in liver stiffness, 6–12 months after completion of anti-viral therapy in those who achieve viral eradication, as compared to pre-treatment liver stiffness.

Temporal evolution of liver stiffness after viral eradication: In order to assess temporal evolution of change in liver stiffness after completion of antiviral therapy, we performed separate analyses based on timing of post-treatment liver stiffness assessment (end of treatment (EOT), within 1–6 months after EOT, including patients with SVR12, 6–12 months after EOT, including patients with SVR24, and >1y after EOT) in patients who achieved viral eradication.

Subgroup and sensitivity analyses: In order to understand stability of association and identify factors that may influence magnitude of change in liver stiffness 6–12m after EOT (or heterogeneity in summary estimate), we performed subgroup analyses based on: (a) type of antiviral therapy (DAAs vs. interferon-based therapies), baseline cirrhosis either based on author-define VCTE cut-off (ranging from 12.5–14.6 kPa) or liver biopsy (>75% of cohort with cirrhosis vs. <75% with cirrhosis), co-infection with HIV (>30% with co-infection HIV vs. 0–30% of cohort), geographic location (Western vs. Asian), and publication type (full-text vs. conference proceedings). Additionally, to understand the impact of baseline factors that may influence change in liver stiffness, we performed meta-regression based on mean BMI of cohort, mean pre-treatment ALT and proportion of cirrhosis. We also performed sensitivity analysis, restricting only to high quality studies.

Secondary Outcomes—To estimate net decline in liver stiffness after viral eradication, we compared the change in liver stiffness in those who achieved SVR vs. those who did not achieve SVR. Finally, we estimated what proportion of patients with pre-treatment liver stiffness >9.5kPa, achieved post-treatment liver stiffness <9.5kPa after SVR.

Statistical Analysis

We used the random-effects model of DerSimonian and Laird to calculate weighted mean difference (WMD) and 95% confidence intervals (CI) between pre- and post-treatment liver stiffness in patients who achieved SVR and those who did not achieve SVR.[8] For all analyses, median was consider equivalent to mean, and IQR was converted to s.d. by dividing by 1.35, and range was transformed to s.d. by dividing by 4, in accordance with the Cochrane manual.[9] Heterogeneity between study-specific estimates was estimated using the inconsistency index (I^2), and cut-offs of <30%, 30%–59%, 60%–75% and >75% suggested low, moderate, substantial and considerable heterogeneity, respectively.[10] Sources of heterogeneity were investigated using subgroup analyses by stratifying original estimates according to study characteristics as described above, or using meta-regression (for continuous variables); p-value of <0.05 was suggestive of the grouping variable being a significant source of heterogeneity. Small study effects were assessed qualitatively using funnel plot asymmetry and quantitatively using the Egger's regression test.[11] All analysis was performed using Comprehensive Meta-Analysis (CMA) version 2 (Biostat, Englewood, NJ).

RESULTS

From a total of 2377 unique studies identified using our search strategy, 23 observational studies, and one post-hoc analysis of an RCT, were included in this analysis.[12–35] Fifteen studies were excluded due to lack of data stratified by SVR status, 22 were excluded due to lack of repeated paired LSM, 15 because conducted on untreated patients (or merged data of treated and untreated cohorts), and 4 due to high drop out rate (>20%).

Characteristics and Quality of Included Studies

Table 1 describes the characteristics of the included studies. We identified 24 observational studies including 2934 patients with HCV with paired VCTE before and after antiviral therapy (2214 patients achieved SVR). Nineteen studies were conducted in Europe, two studies in Japan, and one each in USA, China and Egypt. Of the 24 studies, 15 reported the primary outcome of change in liver stiffness, 6–12 months after completion of antiviral therapy, in 1548 patients who achieved SVR.[12, 13, 16, 17, 19–25, 27, 29, 33, 34] All studies only reported data from reliable VCTE readings (at least 10 validated measurements, and an interquartile range [reflects variations among measurements] of less than 30% of the median value).

Table 2 describes the baseline characteristics of patients in the included studies. The mean age of participants at the time of initial biopsy ranged from 39y to 67y; majority of patients were males. The mean BMI ranged from 22.8 to 27.8kg/m^2, and the mean ALT ranged from 52 to 110IU/L. In included studies, 0 to 89% of patients had baseline cirrhosis; in five studies, >75% of patients had cirrhosis. In three studies, >50% patients were co-infected with HIV. Concomitant diabetes, NAFLD, excessive alcohol use and HBV was inconsistently reported, and when reported, was present in <10% of cohort. Patients were treated with interferon-based therapy in 8 studies, and DAAs in 6 six studies. Overall, 9 studies were deemed to be at low risk of bias (eTable 1).

Change in liver stiffness in patients with viral eradication

At 6–12 months after end of therapy: On pooled analysis of patients who achieved SVR, the mean liver stiffness declined by 3.2 kPa (95% CI, 2.6 to 3.9), as compared to pre-treatment liver stiffness, 6–12 months after EOT, with substantial heterogeneity (I^2=65%) (Figure 2).[12, 13, 16, 17, 19–25, 27, 29, 33, 34] The median relative decline in liver stiffness was 28.2% (interquartile range [IQR], 21.8–34.8) In contrast, mean liver stiffness remained fairly unchanged 6–12 months after EOT in patients who did not achieve SVR (WMD, −0.6; 95% CI, −1.7 to 0.5; p=0.31; 7 studies).

In 4 studies, with 191 patients who achieved SVR and were classified as having ‘cirrhosis’ (based investigator-defined liver stiffness >12.5–14.6kPa or histology) prior to therapy, 26.6% (95% CI, 15.9–40.9%; I^2=61%) patients had decline in liver stiffness to below 9.5kPa.[12, 15, 16, 34] Similarly, from 261 patients who achieved SVR and were classified as having ‘advanced fibrosis or cirrhosis’ (based on liver stiffness >9,5kPa), 47.1% (95% CI, 27.1–68.0; I^2=89%) patients had post-treatment liver stiffness below 9.5 kPa.[12, 15, 16, 22, 34]

Subgroup analysis and Meta-regression: On subgroup analysis, the magnitude of decline in liver stiffness was higher in patients treated with DAAs (WMD, −4.6 kPa; 95% CI, −3.3 to −5.6) as compared to patients treated with interferon-based therapies (WMD, −2.6; 95% CI, −1.9 to −3.4) ($P_{interaction}$=0.03), and in cohorts where the majority of patients had baseline 'cirrhosis' (>75% cirrhosis vs. <75% cirrhosis: WMD, −5.1 kPa vs. −2.8 kPa; $P_{interaction}$=0.02) (Table 3). Of note, while the absolute magnitude of decline was higher in patients with high baseline stiffness, the relative magnitude of decline was comparable. No significant differences were observed based on presence or absence of HIV co-infection or geographic location.

On meta-regression, the magnitude of decline in liver stiffness was dependent on baseline ALT, i.e., cohorts in which patients had higher mean baseline ALT experienced a more significant decline in liver stiffness after SVR, as compared to patients with lower mean ALT (p<0.001) (eFigure 1A). Similarly, cohorts with higher proportion of patients with baseline cirrhosis (or higher pre-treatment liver stiffness) experienced greater absolute decline in liver stiffness (p=0.006) (eFigure 1B). No association was observed between baseline BMI and magnitude of decline in liver stiffness (p=0.34) (eFigure 1C).

Temporal evolution of change in liver stiffness—In assessing temporal evolution of decline in liver stiffness in patients who achieved SVR, liver stiffness declined by 2.4 kPa (95% CI, 1.7–3.0) at EOT (9 studies),[12, 15, 18–20, 23–25, 28, 30], 3.1 kPa (95% CI, 1.6 to 4.6) 1–6 months after EOT (5 studies, including patients with SVR12),[13, 14, 19, 31, 32], and 4.1 kPa (95% CI, 3.3 to 4.9) >12 months after completion of antiviral therapy (8 studies) (Figure 3).[12, 15–17, 24–26, 28, 35] Overall, this change in stiffness over time was statistically significant (p=0.014). In contrast, mean liver stiffness at EOT and >12m after completion of antiviral therapy in those without SVR was unchanged as compared to pre-treatment liver stiffness (EOT: WMD, −0.5 [95% CI, −1.5 to 0.5]; >12m after EOT: WMD, 0.9 [95% CI, −1.9 to 3.2]). In comparing patients who achieved SVR vs. no SVR, the overall difference in magnitude of decline in liver stiffness was −3.3 kPa (95% CI, −2.2 to −4.6) at 6–12 months after completion of therapy. This magnitude of difference also increased with increasing time since antiviral therapy (p=0.003) (eFigure 2).

Sensitivity Analysis and Publication Bias—The primary results were unchanged on sensitivity analysis restricted to high quality studies (change in liver stiffness in patients with SVR, 6–12m after EOT: −3.0 [95% CI, −2.1 to −3.9]). There was no evidence of small study effects quantitatively based on funnel plot, or qualitatively based on Egger's test (p=0.27).

DISCUSSION

Through a systematic review of 24 studies with paired liver stiffness measurement using VCTE, before and after antiviral therapy, we made several key observations. First, liver stiffness decreases significantly, by approximately 3.1 kPa, in 6–12 months after achieving viral eradication; in contrast, liver stiffness remains unchanged in patients who do not achieve SVR. The median decline in liver stiffness was 28.2%, with an interquartile range of 21.8% to 34.8%. Approximately 47% of patients with baseline liver stiffness in the advanced fibrosis or cirrhosis range (>9.5kPa), have post-treatment liver stiffness below 9.5kPa.

Second, in patients who achieve SVR, the magnitude of decline in liver stiffness is incremental over time after completion of therapy, increasing progressively from −2.4 kPa at EOT to −4.1kPa at 12 months and beyond. Third, the magnitude of decline in liver stiffness is higher in patients with high baseline liver stiffness, patients treated with DAAs (vs. patients treated with interferon-based therapies), and patients with high baseline aminotransferases (a marker of hepatic inflammation prior to therapy). These findings are directly applicable to patient care and health policy. Since increasing numbers of patients are seeking care and are being cured of HCV, estimation of magnitude of decline in liver stiffness non-invasively after viral eradication may help identify patients likely to be at low risk of liver-related complications (for example, non-cirrhotic patients with post-treatment liver stiffness <9.5kPa), although robust evidence of how decline in liver stiffness correlates with improvement in clinically relevant outcomes is very limited.

With increasing reliance on non-invasive modalities for fibrosis assessment in patients with chronic liver diseases, and ease of serial measurement, assessment of change in liver stiffness is perhaps more relevant than change in fibrosis stage. Decline in liver stiffness following viral eradication is probably a combination of resolution of hepatic inflammation, as well as regression of fibrosis; it is probable that early decline is largely related to resolution of inflammation, whereas continued decline beyond 1 year after EOT may be related to fibrosis regression, as has been observed with paired liver biopsy studies with interferon-based therapy.[36, 37] However, detailed prospective studies are warranted to evaluate short- and long-term implications of rapidity and magnitude of decline in liver stiffness with anti-viral therapy. While progressive increase in liver stiffness has been associated with worsening liver-related complications regardless of fibrosis stage, at this time, it is conjectural that decline in liver stiffness will likely translate into lower risk of liver-related complications.

We observed a greater magnitude of decline in liver stiffness in patients who achieved SVR with DAAs vs. interferon-based therapy. This may be related to more rapid clearance of viremia observed with DAAs, with associated rapid decline in hepatic inflammation and fibrogenesis, or potentially higher baseline stiffness in DAA-treated patients resulting in greater magnitude of decline in stiffness. We also observed a greater magnitude of decline in liver stiffness in patients with higher baseline liver stiffness, as compared to those with lower baseline stiffness, and in those with higher baseline ALT. This may be a reflection of higher hepatic inflammatory burden, which responds rapidly to effective antiviral therapy, causing a larger magnitude of change in stiffness, although its clinical significance in terms of more favorable long-term outcomes is still unclear. It is important to note that in cohorts with higher median baseline stiffness, while the absolute decline in liver stiffness with SVR was higher (as compared to cohorts with lower median stiffness), the relative magnitude of decline in stiffness was more homogeneous (28.2% decline [IQR, 21.8–34.8]). We did not observe any significant difference in change in stiffness based on BMI, on meta-regression. There was very limited data on co-existing diabetes, NAFLD or alcohol consumption, so the potential impact of these ongoing hepatic insults on change in liver stiffness remains to be seen.

The strengths of our systematic review include a (a) comprehensive and systematic literature search with well-defined and restrictive inclusion criteria (limiting to studies in which >80% patients underwent post-treatment VCTE), (b) stratification of analyses by SVR status allowing for comparative assessment, although the number of SVR patients was considerably higher due to the inclusion of several studies reporting only on patients with SVR, (c) recognizing temporal evolution of liver stiffness following SVR and *a priori* determining primary time point of analysis, (d), rigorous evaluation of study quality which has been used as the basis for sensitivity analysis, (e) assessment of multiple, clinically relevant end points, and (f) performing several pre-planned subgroup and sensitivity analyses and meta-regression accounting for key determinants of change in liver stiffness. However, there are several limitations in our meta-analysis. First, we did not have access to individual participant data, and hence all analyses were performed at study-level, using mean or median liver stiffness pre- and post-therapy to inform magnitude of change in stiffness. Moreover, patients recruited in the studies conducted with DAAs presented higher baseline liver stiffness, which may play a role in the greater magnitude in decline in liver stiffness observed in this subgroup. Second, timing of VCTE post-SVR was also based on mean/median time, as opposed to a fixed time point at which all patients underwent assessment; hence, we used ranges of time of post-treatment VCTE assessment in reporting our analyses. Third, follow-up assessment after SVR was relatively short, hence, long-term evolution of liver stiffness after antiviral therapy and impact of decline in liver stiffness on patient clinical outcomes could not be ascertained. Fourth, studies did not consistently report potential confounders like NAFLD, diabetes, alcohol consumption which may influence liver stiffness. When variables were available, such as co-infection with HIV or mean BMI, we performed sub-group analysis or meta-regression, and observed no significant impact on magnitude of decline in stiffness. Finally, our systematic review focused only on VCTE, and not other modalities of liver stiffness assessment such as shear-wave elastography or acoustic radiation force impulse.[38,39]

In conclusion, liver stiffness measured using VCTE declines significantly after achieving SVR (median, 28.2%), and the magnitude of decline is incremental with time since antiviral therapy. Magnitude of decline is higher in patients treated with DAAs, and in patients with higher baseline stiffness. Approximately 47% of patients with baseline classification of having advanced fibrosis or cirrhosis range liver stiffness, may have decline of post-treatment liver stiffness to <9.5kPa. With this decline in liver stiffness, it is conceivable that risk of liver-related complications would decrease, particularly in non-cirrhotic patients. Future research is warranted on the impact of magnitude and kinetics of decline in liver stiffness on improvement in liver-related outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol. 2015; 63:199–236. [PubMed: 25911336]
2. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. Hepatology. 2015; 62:932–54. [PubMed: 26111063]
3. Smith BD, Morgan RL, Beckett GA, et al. Hepatitis C virus testing of persons born during 1945–1965: recommendations from the Centers for Disease Control and Prevention. Ann Intern Med. 2012; 157:817–22. [PubMed: 22910836]
4. Hoefs JC, Shiffman ML, Goodman ZD, et al. Rate of progression of hepatic fibrosis in patients with chronic hepatitis C: results from the HALT-C Trial. Gastroenterology. 2011; 141:900–908. e1–2. [PubMed: 21699796]
5. Singh S, Fujii LL, Murad MH, et al. Liver stiffness is associated with risk of decompensation, liver cancer, and death in patients with chronic liver diseases: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2013; 11:1573–84. e1–2. quiz e88–9. [PubMed: 23954643]
6. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015; 4:1. [PubMed: 25554246]
7. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2012
8. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7:177–88. [PubMed: 3802833]
9. Higgins, JPT., Altman, DG., Sterne, JAC. Cochrane Handbook for Systematic Reviews of Interventions. Higgins, JPT., Green, S., editors. The Cochrane Collaboration; 2011. Available from http://www.cochrane-handbook.org
10. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003; 327:557–60. [PubMed: 12958120]
11. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315:629–34. [PubMed: 9310563]
12. Arima Y, Kawabe N, Hashimoto S, et al. Reduction of liver stiffness by interferon treatment in the patients with chronic hepatitis C. Hepatol Res. 2010; 40:383–392. [PubMed: 20236358]
13. Bachofner JA, Valli PV, Kroger A, et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int. 2017; 37:369–376. [PubMed: 27678216]
14. Bernuth S, Yagmur E, Schuppan D, et al. Early changes in dynamic biomarkers of liver fibrosis in hepatitis C virus-infected patients treated with sofosbuvir. Dig Liver Dis. 2016; 48:291–7. [PubMed: 26514736]
15. Carton JA, Collazos J, de la Fuente B, et al. Course of liver fibrosis in HIV-hepatitis C virus-coinfected patients depending on the response to hepatitis C therapy. AIDS Res Hum Retroviruses. 2013; 29:215–22. [PubMed: 22734850]
16. Chekuri S, Nickerson J, Bichoupan K, et al. Liver Stiffness Decreases Rapidly in Response to Successful Hepatitis C Treatment and Then Plateaus. PLoS One. 2016; 11:e0159413. [PubMed: 27442255]
17. Crisan D, Radu C, Grigorescu MD, et al. Prospective non-invasive follow-up of liver fibrosis in patients with chronic hepatitis C. J Gastrointestin Liver Dis. 2012; 21:375–82. [PubMed: 23256120]
18. El Saadany SSH, ZIada DH, Hamisa M, Hefeda M, Selim A, Goraba H. Fibroscan versus liver biopsy in the evaluation of response among the Egyptian HCV infected patients to treatment. Egypt J Radiol Nuc Med. 2016; 47:1–7.
19. Hezode C, Castera L, Roudot-Thoraval F, et al. Liver stiffness diminishes with antiviral response in chronic hepatitis C. Aliment Pharmacol Ther. 2011; 34:656–663. [PubMed: 21752038]
20. Knop V, Hoppe D, Welzel T, et al. Regression of fibrosis and portal hypertension in HCV-associated cirrhosis and sustained virologic response after interferon-free antiviral therapy. J Viral Hepat. 2016; 23:994–1002. [PubMed: 27500382]

21. Macias J, del Valle J, Rivero A, et al. Changes in liver stiffness in patients with chronic hepatitis C with and without HIV co-infection treated with pegylated interferon plus ribavirin. J Antimicrob Chemother. 2010; 65:2204–11. [PubMed: 20656678]
22. Mandorfer M, Schwabl P, Steiner S, et al. Interferon-free treatment with sofosbuvir/daclatasvir achieves sustained virologic response in 100% of HIV/hepatitis C virus-coinfected patients with advanced liver disease. AIDS. 2016; 30:1039–47. [PubMed: 26760453]
23. Martinez SM, Foucher J, Combis JM, et al. Longitudinal liver stiffness assessment in patients with chronic hepatitis C undergoing antiviral therapy. PLoS ONE [Electronic Resource]. 2012; 7:e47715.
24. Martini S, Sacco M, Strona S, et al. Impact of viral eradication with sofosbuvir-based therapy on the outcome of post-transplant hepatitis C with severe fibrosis. Liver Int. 2016
25. Ogawa E, Furusyo N, Toyoda K, et al. The longitudinal quantitative assessment by transient elastography of chronic hepatitis C patients treated with pegylated interferon alpha-2b and ribavirin. Antiviral Res. 2009; 83:127–134. [PubMed: 19443053]
26. Qing S, Ji D, Li B, et al. Improvement of glucose and lipid metabolism with pegylated interferon-a plus ribavirin therapy in Chinese patients chronically infected with genotype 1b hepatitis C virus. Ann Saudi Med. 2015; 35:293–7. [PubMed: 26497709]
27. Saez-Royuela F, Linares P, Cervera LA, et al. Evaluation of advanced fibrosis measured by transient elastography after hepatitis C virus protease inhibitor-based triple therapy. Eur J Gastroenterol Hepatol. 2016; 28:305–12. [PubMed: 26636405]
28. Stasi C, Arena U, Zignego AL, et al. Longitudinal assessment of liver stiffness in patients undergoing antiviral treatment for hepatitis C. Dig Liver Dis. 2013; 45:840–3. [PubMed: 23660078]
29. Bruno G, Dell'Acqua R, Milano E, et al. Early regression of liver fibrosis in HCV infected patients with or without HIV infection after treatment with DAAs. Hepatology. 2016; 64:326A.
30. Iacob S, Popescu I, Gheorghe L. 100% Virological response with 3D regimen and significant short-term liver stiffness improvement in patients with recurrent hepatitis C following liver transplantation. Hepatology. 2016; 64:809A.
31. Stradella D, Gaia S, Vanni E, et al. Early evaluation of liver disease severity with non-invasive tests in the era of new direct acting antiviral drugs (DAAs): a pilot study. Hepatology. 2016; 64:328A. [PubMed: 27178231]
32. Gamal N, Brodosi L, Scuteri A, et al. Liver stiffness measurments using fibroscan after three months of IFN-based antiviral therapy is unlikely to predict viral response in cirrhotic patients. Journal of Hepatology. 2015; 62:S506–S507.
33. Lens S, Alvarado-Tapias E, Marino Z, et al. Impact of all-oral antiviral therapy on portal pressure and hemodynamics on HCV-infected cirrhotic patients. Hepatology. 2016; 64:30A–31A.
34. Bourliere M, Loustaud-Ratti V, Metivier S, et al. Changes in liver stiffness by transient elastography (TE) and serum lysyl oxidase-like-2 (sLOXL2) in patients with cirrhosis treated with ledipasvir/sofosbuvir (LDV/SOF)-based therapy. Hepatology. 2015; 62:596A–597A.
35. Fransen van de Putte DE, Fischer K, de Knegt RJ, et al. Beneficial effect of successful HCV treatment in patients with inherited bleeding disorders, assessed by liver stiffness measurements. Haemophilia. 2012; 18:e266–72. [PubMed: 22103568]
36. Shiratori Y, Imazeki F, Moriyama M, et al. Histologic improvement of fibrosis in patients with hepatitis C who have sustained response to interferon therapy. Ann Intern Med. 2000; 132:517–24. [PubMed: 10744587]
37. Toccaceli F, Laghi V, Capurso L, et al. Long-term liver histology improvement in patients with chronic hepatitis C and sustained response to interferon. J Viral Hepat. 2003; 10:126–33. [PubMed: 12614469]
38. Suda T, Okawa O, Masaoka R, et al. Shear wave elastography in hepatitis C patients before and after antiviral therapy. World J Hepatol. 2017; 9:64–68. [PubMed: 28105260]
39. Forestier N, Gaus A, Herrmann E, et al. Acoustic radiation force impulse imaging for evaluation of antiviral treatment response in chronic hepatitis C. J Gastrointestin Liver Dis. 2012; 21:367–73. [PubMed: 23256119]

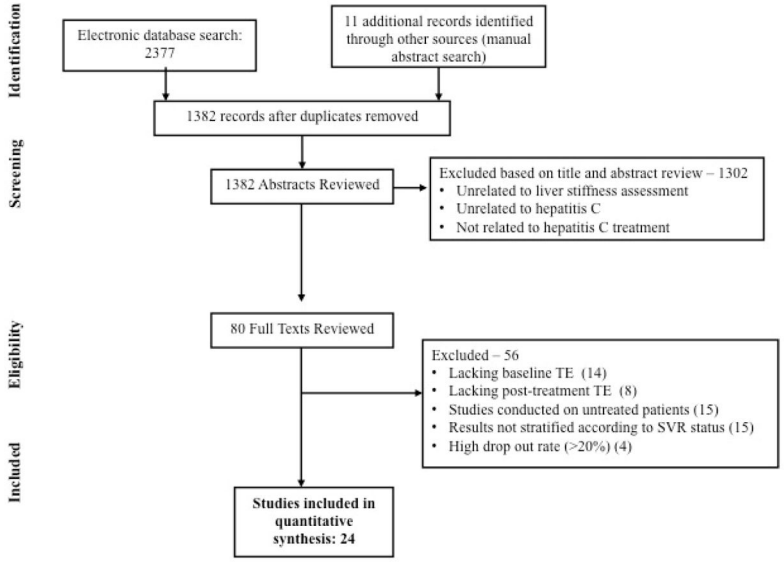

Figure 1.
Study Selection Flowsheet

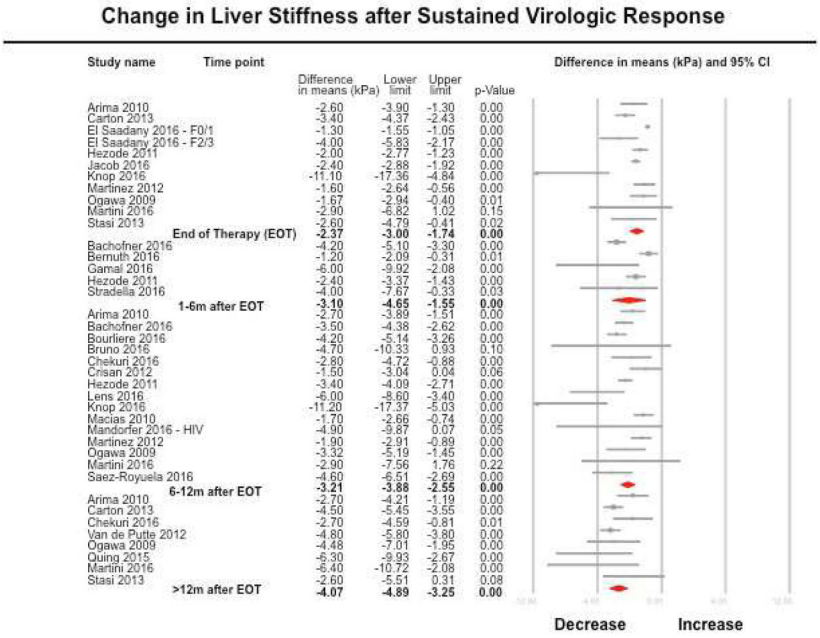

Figure 2.

Forest plot with individual studies showing magnitude and kinetics of decline in liver stiffness in patients with HCV who achieve sustained virologic response, as compared to baseline, prior to anti-viral therapy

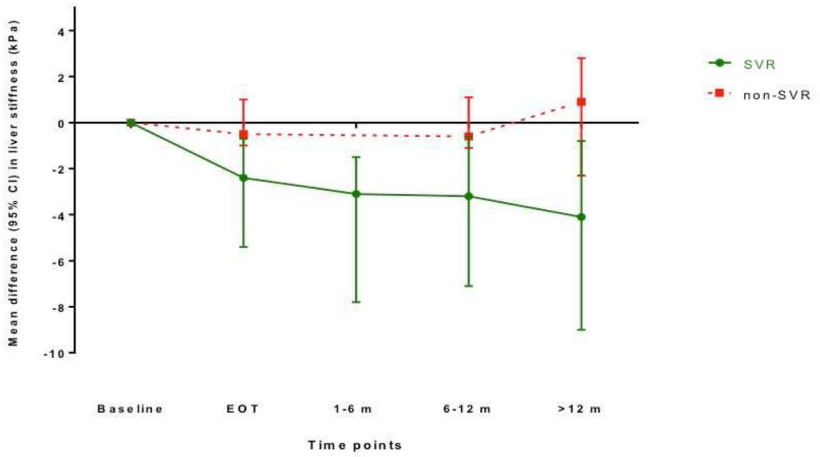

Figure 3.

Comparison of change in liver stiffness over time, in patients with HCV who achieve SVR vs. patients who do not achieve SVR

Table 1

Characteristics of included observational studies assessing change in liver stiffness change in chronic hepatitis C patients.

Study, Year	Location; Time period; Follow-up	Treatment; Duration; N	Biopsy (N); Cirrhosis based on biopsy	SVR/nSVR	Interval end of therapy-LSM (months); N with multiple assessments	Baseline LSM (IQR)
Arima, 2010[12]	Japan; 2005–2008; 2 years	IFN±Ribavirin; 24, 48 or 72 weeks according to genotype; 145	142; 23	93/52	0, 1 year and 2 years; 142	SVR pts: 8 (5–11.9); relapsers: 10.6 (7–16.6) nSVR pts: 9.9 (5.7–15.7)
Bachofner, 2016[13]	Switzerland; 2013–2015; 40 weeks	DAAs; 15.67 weeks (mean); 392	222; 52	365/27	12 weeks, and 40 weeks; 392 at 12 weeks and 143 at 40 weeks	Overall: 12.65 (9.45–19.2) SVR pts: 12.5 (9.2–18.2) nSVR pts: 19.4 (10.8–32.5)
Bernuth, 2016[14]	Germany; 2014; 12 weeks	DAAs ± IFN; 12 weeks; 32	NR; NR	30/2	0, and 12 weeks; 29	8 (6.7–9.5)
Bourliere, 2015[a34]	France; NR; 24 weeks	DAAs; 12 or 24 weeks; 137	NR; NR	137/0	24 weeks; 137	17.5 (14.3–26.3)
Bruno, 2016[a29]	Italy; NR; 24 weeks	DAAs; NR; 84	NR; NR	84/0	24 weeks; 84	15.5 (7–35)
Carton, 2013[15]	Spain; 2002–2010; 2 years	IFN±Ribavirin; NR; 210 (only 90 with LSM)	141; 51	80 (39 with LSM)/130 (51 with LSM)	0 and 2 years; 90	SVR pts: 10.2 (7.6–12.5) nSVR pts: 10.2 (7.6–20.5)
Chekuri, 2016[16]	USA; 2008–2016; 1.7 years	IFN+Ribavirin (52 pts); DAAs (48 pts); NR; 100	None; 0	100/0	24 weeks, and 1.67 year (median); 100 at 24 weeks and 56 at > 1 year	10.4 (7.25–18.6)
Crisan, 2012[17]	Romania; 2008–2010; 24 weeks	IFN+Ribavirin; 48 weeks; 179	179; 38	99/80	24 weeks; 179	SVR pts: 7 (95% CI: 6–8.57) nSVR pts: 10 (8.56–12.53)
El Saadany, 2016[18]	Egypt; 2012–2014; until EOT	IFN+Ribavirin; 48 weeks; 300	300; 0	167/133	0 weeks; 300	F0/1 pts: 5.7±1.12 (mean±SD) F2/3 pts: 11.4±6.25
Fransen Van de	Holland;	IFN+Ribavirin; NR; 17	None; 0	17/0	2.5 years (IQR: 1.8–2.8); 17	10.3
Putte, 2012[35]	2005–2009; 2.5 years					
Gamal, 2016[a32]	Italy; 2015; 12 weeks	DAAs; NR; 50	None; 0	50/0	12 weeks; 50	21.6 ±10
Hezode, 2011[19]	France; 2005–2007; 24 weeks	IFN+Ribavirin; 12 or 24 weeks according to genotype; 91	None; 0	59/32	0, 12 weeks, and 24 weeks; 91	11.1 (8.4–16.3)
Iacob, 2016[a30]	Romania; NR; until EOT	DAAs; NR; 72	NR; NR	72/0	End of treatment; 72	11.9±1.8
Lens, 2016[a33]	Spain; NR; 24 weeks	DAAs; NR; 82	NR; NR	82/0	24 weeks; 82	31±15
Knop, 2016[20]	Germany; 2014–2015; 24 weeks	DAAs; 12 or 24 weeks according to genotype; 54	None; 0	54/0	0, and 24 weeks; 54	32.4 (range: 9.1–75)
Macias, 2010[21]	Spain; 2006–2008; 24 weeks	IFN+Ribavirin; 24 or 48 weeks according to genotype; 143	None; 0	80/63	24 weeks; 143	8.1 (6.2–11.4)

Study, Year	Location; Time period; Follow-up	Treatment; Duration; N	Biopsy (N); Cirrhosis based on biopsy	SVR/nSVR	Interval end of therapy-LSM (months); N with multiple assessments	Baseline LSM (IQR)
Mandorfer, 2016[22]	Austria; NR; 42±2.8 weeks	DAAs; 12 or 24 weeks according to genotype; 31	None; 0	31/0	32.7±1.2 weeks; 31	11.8 (11.5)
Martinez, 2012[23]	Spain/France/Italy; 2008–2009; 72 weeks	IFN+Ribavirin; 24 or 48 weeks according to genotype; 323	189; 32	202/121	0 and 24 weeks; 323	10.6 ± 8.9
Ogawa, 2009[25]	Japan; NR; 96 weeks	IFN+Ribavirin; 24 or 48 weeks according to genotype; 126	118; 16	57/69	0, 48, and 96 weeks; 126	SVR pts: 10.3±4.8 nonSVR pts: 10±5.5
Qing, 2015[26]	China; 2011–2012; 72 weeks	IFN+Ribavirin; 48 weeks; 116	None; 0	90/26	72 weeks; 116	SVR pts: 11.3 (7.3–14.2) nSVR pts: 10.2 (9.7–10.9)
Martini, 2016[24]	Italy; 2014–2015; 48 weeks	DAAs; 12 or 24 weeks according to genotype; 126	28; 25	102; 24	0, 24, and 48 weeks; 126	SVR pts: 20.4 (IQR: 16–33.8); nSVR pts: 28 (21.6–44.4)
Saez-Royuela, 2016[27]	Spain; 2012–2013; 24 weeks	IFN+Ribavirin+Boceprevir or Telaprevir; 48 weeks; 90	None; 0	64/26	24 weeks; 90	13.9 (10.9–21.1)
Stasi, 2013[28]	Italy; 2007–2011; 3 years	IFN+Ribavirin; 24 or 48 weeks according to genotype; 74	21; 1	55/19	0 weeks, and 3 years; 74 at 0 weeks, and 49 at 3 years	SVR pts: 9.5±6.88 nSVR pts: 9.71±4.26
Stradella, 2016[a31]	Italy; 2015; 12 weeks	DAAs; NR; 86	NR; NR	85/1	12 weeks; NR	18±12

[a]Data reported as congress abstracts.

[Abbreviations: DAAs-Direct Antiviral Agents, EOT-End Of Treatment, IFN-Interferon, IQR-Interquartile Range, LSM-Liver Stiffness Measurement, NR-Not Reported, SVR-Sustained Virologic Response, nSVR – no Sustained Virologic response]

Table 2

Baseline characteristics of patients included in observational studies assessing liver stiffness change after antiviral therapy in chronic hepatitis C patients.

Study, Year	Age (IQR)		Sex Male (%)		BMI (IQR)		HIV (%)		Genotype (1/2/3/4)		Viral load (IQR)		AST/ALT Baseline (IQR)	
	SVR	nSVR	SVR	nSVR	SVR	nSVR	SVR	nSVR	SVR	nSVR	SVR	nSVR	SVR	nSVR
Arima, 2010[12]	55 (55.3–69.8)	56 (49.5–62.5)	61 (65.5)	18 (34.6)	NR		None		44/48/1/0	44/8/0/0	850 (158–2405) KIU/mL	1550 (645–2850) KIU/mL	48 (29–70.3)/65 (43.8–97.5)	47.5 (31.5–64)/52 (31.5–75)
Bachofner, 2016[13]	55 (49–64)	57 (53–62)	229 (62.7)	21 (72.4)	24.9 (22.5–28)	27.8 (25.4–30.9)	28 (7.7)	2 (7.4)	232/33/63/37	12/3/7/5	6.09 (6–6.54) log_{10}IU/mL	6.63 (5.9–6.7) log_{10}IU/mL	NR	
Bernuth, 2016[14]	54.5 (49–58)		18 (56.2)		23.5 (22.4–28.6)		1 (3.1)		22/6/3/1		1.7×10^6 IU/mL (1.2×10^6–1.8×10^6)		51 (44.5–63)/59 (50–80.5)	
Bourliere, 2015[a34]	56 (50–62)		NR		26.4 (23.8–29)		None		NR		NR		NR	
Bruno, 2016[a29]	NR		NR		NR		31 (36.9)		NR		NR		NR	
Carton, 2013[15]	43.9 (40.3–47.8)	45.4 (42.2–48.8)	60 (75)	102 (78.5)	NR		80 (100)	130 (100)	1+4: 25 2+3: 55	1+4: 89 2+3: 41	5.84 (5.11–6.22) log_{10}IU/mL	6.28 (5.8–6.65) log_{10}IU/mL	NR	
Chekuri, 2016[16]	60 (54–64)		72 (72)		25.8 (23.3–28.6)		None		85/10/5/0		NR		58 (38–94)/72 (46–125)	
Crisan, 2012[17]	50.7±10.7	49.3±9.6	29 (29.3)	28 (35)	26.3±4.6	27.3±5.1	None		99/0/0/0	80/0/0/0	1.09 × 10^6 IU/mL (0.62–1.52)	1.28 × 10^6 IU/mL (1.06–1.78)	47.5 (37.4–59.5)/70 (53.6–86.4)	58.5 (51.6–66.3)/87 (72.3–105.7)
El Saadany, 2016[18]	1: 43.6±8.9 2: 46.6±8		1: 95 (63.3) 2: 106 (70.6)		NR		None		NR		NR		NR	
Fransen Van de Putte, 2012[35]	39 (range: 20–58)		16 (94)		25 (22.4–26.6)		None		12/0/4/1		NR		NR	
Gamal, 2016[a32]	66.8±10.2		64%		54% with BMI > 25		NR		NR		NR		NR	
Hezode, 2011[19]	52.4±11.6		63 (69.2)		24.9 ±3.5		None		1+4: 49 2+3: 42		5.8 log_{10}IU/mL (5.2–6.2)		NR/101 (63–153)	
Iacob, 2016[a30]	55.2±7		40 (55.5)		NR		NR		NR		NR		NR	
Lens, 2016[a33]	NR		NR		NR		NR		NR		NR		NR	
Knop, 2016[20]	57 (range: 30–86)		37 (68.5)		26.1 (range: 19–44)		2 (3.7)		36/0/13/5		6.35±6.43 log_{10}IU/mL		82 (range: 17–260)/71 (range: 17–254)	
Macias, 2010[21]	42 (38–45)		114 (80)		NR		97 (67.8)		82/3/45/15		6.52 log_{10}IU/mL (5.83–6.96)		NR/57 (36–84)	
Mandorfer, 2016[22]	49.2 ±1.4		20 (64.5)		NR		31 (100)		21/0/7/3		NR		NR	
Martinez, 2012[23]	48.5±11.2		214 (66.3)		24.6 ±3.4		None		186/41/76/17		5.8 log_{10}IU/mL ± 0.9		AST/ULN: 1.9 ±1.4 ALT/ULN: 2.7 ± 2.7	
Ogawa, 2009[25]	52.7±13.2	60.3±9.3	30 (52.6)	25 (36.2)	23.1±3.1	22.8±3.1	None		34/23/0/0	65/4/0/0	1565±1645 KIU/mL	2014±1455 KIU/mL	65±39.2/88.3±73.7	65.8±42.4/72.7±53.2
Qing, 2015[26]	44 (35–50.8)	40 (35–53)	57 (63.3)	14 (53.8)	26.9 (24.6–29.3)	25.7 (24.5–28.4)	None		90/0/0/0	26/0/0/0	6.09 log_{10}IU/mL (1.26)	6.17 log_{10}IU/m L (0.85)	NR/88.7 (88.4)	NR/66.4 (45.7)
Martini, 2016[24]	60 (54–66)		99 (78.6)		24.6 (22.5–26.9)		None		94/6/21/6		6.4 log_{10}IU/mL (6.1–6.6)		60 (40–101)/69 (45–116)	
Saez-Royuela, 2016[27]	52.4 ±8.6		70 (77.7)		25.7 ±3.9		None		90/0/0/0		6.3 log_{10}IU/mL (5.9–6.6)		NR/87 (60–125.5)	
Stasi, 2013[28]	51.09±12.84		43 (58.1)		24.63±3.5		None		1+4: 32 2+3: 42		6.52 log_{10}IU/mL ±6.73		73.36±55.06/110.39±86.5	

Study, Year	Age (IQR)		Sex Male (%)		BMI (IQR)		HIV (%)		Genotype (1/2/3/4)		Viral load (IQR)		AST/ALT Baseline (IQR)	
	SVR	nSVR	SVR	nSVR	SVR	nSVR	SVR	nSVR	SVR	nSVR	SVR	nSVR	SVR	nSVR
Stradella, 2016[a31]	58±10		63%		25.1 ±4.1		NR		73%/11%/7%/9%		NR		NR/90±66	

[a]Data reported as congress abstracts.

[*]The whole cohort was composed of SVR patients.

[≠]Data stratified according to fibrosis stage (group 1: F0/1; group 2: F2/3)

[α]Data not stratified according to SVR status

[Abbreviations: ALT-Alanine aminotransferase, AST-Aspartate aminotransferase, BMI-Body Mass Index, HIV-Human Immunodeficiency Virus, IQR-Interquartile Range, NR-Not Reported, SVR-Sustained Virological Response, ULN-Upper Limit of Normal]

Table 3

Subgroup analysis, evaluating sources of heterogeneity in the magnitude of decline in liver stiffness 6–12 months after therapy in patients who achieve SVR.

Subgroup		No. of studies	Change in liver stiffness (kPa)	Within-group heterogeneity (I^2)	P-interaction
Antiviral therapy	**Interferon-based therapy**	**8**	**−2.63 (−1.91 to −3.36)**	**59%**	**0.03**
	Direct acting antivirals	**6**	**−4.46 (−3.32 to −5.59)**	**45%**	
Co-infection with HIV (>30% with HIV)	Yes	3	−2.41 (−0.51 to −4.31)	20%	0.37
	No	12	−3.33 (−2.65 to −4.02)	63%	
Primarily patients with cirrhosis (>75%)	**Yes**	**5**	**−5.07 (−3.26 to −6.87)**	**40%**	**0.02**
	No	**10**	**−2.79 (−2.18 to −3.41)**	**56%**	
Location	Western	13	−3.30 (−2.52 to −4.08)	69%	0.52
	Asian	2	−2.88 (−1.88 to −3.88)	0%	
Publication type	**Full text**	**12**	**−4.42 (−3.53 to −5.29)**	**60%**	**0.01**
	Abstract	**3**	**−2.90 (−2.23 to −3.57)**	**0%**	