Criteria Grid
Hepatitis C Research Studies, Tools, and Surveillance Systems

Best Practice/Intervention:	Eslam M. et al. (2011) Meta-analysis: insulin resistance and sustained virological response in hepatitis C. *Alimentary Pharmacology & Therapeutics*, 34(3):297-305
Date of Review:	March 11, 2015
Reviewer(s):	Christine Hu

Part A

Category:	**Basic Science** ☐ **Clinical Science** ☐ **Public Health/Epidemiology** ☐ **Social Science** ☐ **Programmatic Review** ☒
Best Practice/Intervention:	**Focus:** **Hepatitis C** ☒ **Hepatitis C/HIV** ☐ **Other:** **insulin resistance** **Level:** **Group** ☒ **Individual** ☐ **Other:** **Target Population:** **HCV treatment-naive patients** **Setting:** **Health care setting/Clinic** ☒ **Home** ☐ **Other:** **Country of Origin:** **Spain** **Language:** **English** ☒ **French** ☐ **Other:**

Part B

	YES	NO	N/A	COMMENTS
Is the best practice/intervention a meta-analysis or primary research?	☒	☐	☐	meta-analysis; to evaluate, quantify and summarize the impact of homeostasis model assessment of insulin resistance (HOMA-IR) on sustained virological response rate in HCV treatment-naive patients
Has the data/information been used for decision-making (e.g. program funding developments, policies, treatment guidelines, defining research priorities and funding)?	☐	☒	☐	Given the limitations of the heterogeneity in the studies' determination and calculation of HOMA-IR, article suggests better handling and interpretation of HOMA is required until new tools for assessing insulin resistance are developed.
Do the methodology/results described allow the reviewer(s) to assess the generalizability of the	☒	☐	☐	

results?				
Are the best practices/methodology/results described applicable in developed countries?	☒	☐	☐	
	YES	**NO**	**N/A**	**COMMENTS**
Are the best practices/methodology/results described applicable in developing countries?	☒	☐	☐	
The research study/tool/data dictionary is easily accessed/available electronically	☒	☐	☐	Available for download from http://onlinelibrary.wiley.com
Is there evidence of cost effective analysis with regard to interventions, diagnosis, treatment, or surveillance methodologies? If so, what does the evidence say? ***Please go to Comments section***	☐	☒	☐	
Are there increased costs (infrastructure, manpower, skills/training, analysis of data) to using the research study/tool/data dictionary?	☐	☒	☐	
How is the research study/tool funded? ***Please got to Comments section***	☐	☒	☐	Study was not funded
Is the best practice/intervention dependent on external funds?	☐	☒	☐	
Other relevant criteria: _____	☐	☐	☐	- Main endpoint: SVR rate, defined as percentage of patients with undetectable HCV RNA 24 weeks after completion of therapy - Insulin resistance is associated with approx. threefold increase in risk of failure to achieve SVR when treatment naive patients were treated with Peg-IFN and RBV
WITHIN THE SURVEILLANCE SYSTEM FOR REVIEW				
Are these data regularly collected?	☐	☒	☐	only searched studies published through December 2010

Are these data regularly collected at and/or below a national level?	☐	☒	☐	
Are these data collected manually or electronically?	☐	☐	☐	Electronically: searched MEDLINE and EMBASE
RESEARCH REPORTS				
Has this research been published in a juried journal?	☒	☐	☐	*Alimentary Pharmacology & Therapeutics*
Does the evidence utilize the existing data/surveillance information or has it generated new data and/or information?	☐	☐	☐	Utilize existing data/surveillance information: 14 published articles included in review

AP&T Alimentary Pharmacology and Therapeutics

Meta-analysis: insulin resistance and sustained virological response in hepatitis C

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As part of AP&T's peer-review process, a technical check of this meta-analysis was performed by Dr. P. Collins.

SUMMARY

Background
A higher baseline homeostasis model assessment of insulin resistance (HOMA-IR) score has sometimes predicted a poorer sustained virological response (SVR) rate to peginterferon/ribavirin therapy in treatment-naïve chronic hepatitis C patients.

Aim
To perform a meta-analysis to evaluate the impact of HOMA-IR on SVR in hepatitis C.

Methods
Relevant studies were identified by searching Medline and EMBASE. We identified 17 publications that addressed the influence of insulin resistance on SVR. The random effect model of Der Simonian and Laird method were used for heterogeneous studies using the Meta-Disc software 1.4, Madrid, Spain.

Results
Normal insulin sensitivity was associated with a higher rate of SVR [odds ratio (OR) 2.86 (95%CI: 1.97–4.16)] in comparison with insulin resistance. Moreover, in separate analysis by genotype selecting studies that used HOMA-IR > 2 as cut-off defining insulin resistance, SVR was higher in patients with HOMA-IR < 2 in all genotypes: HCV-1 [OR: 2.16 (95%CI: 1.51–3.08)], HCV-2&3 [OR: 3.06 (95%CI: 1.06–8.82)] and HCV-4 [OR: 6.65(95%CI: 2.51–17.61)]. Studies reporting no association between HOMA and SVR included easy-to-cure cohorts, analysed variables strongly related with insulin resistance like body mass index, steatosis, hyper γGT, age and fibrosis and reported differences in handling and interpretation of HOMA-IR.

Conclusion
Elevated HOMA-IR was associated with a lower cure rate of patients with hepatitis C treated with Peg-IFN-α/ribavirin irrespective of genotype, and the more difficult-to-treat cohort, the better the HOMA-IR prediction. HOMA-IR is, as a surrogate marker of insulin resistance, susceptible to some biases derived from both handling and interpretation.

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INTRODUCTION

Worldwide, approximately 200 million people are chronically infected with hepatitis C virus.[1] Chronic HCV infection is characterized by a high rate of fibrosis progression, leading to cirrhosis and ultimately to hepatocellular carcinoma.[2, 3] Combination therapy with pegylated interferon alpha and ribavirin (Peg-IFN/RBV) represents the current standard of care in chronic HCV.[4, 5] Despite the improvements in sustained virologic response (SVR) seen using combination of Peg-IFN plus weight-based RBV, SVR rates in genotypes 1 and 4 populations have remained unsatisfactory with reported SVR rates of 28.9–54%.[6, 7] Even more unsatisfactory SVR rates on the order of 10–20% have been seen in difficult-to-treat populations such as African Americans, Hispanics or insulin-resistant patients.[6–8] Studying the factors influencing SVR in patients with HCV treated with Peg-IFN/RBV has been assiduously pursued over the past two decades. Now, there is a great interest by the importance of host factors such as fibrosis progression, genetic factors and metabolic disorders, and these have been invoked to explain the reported differences in SVR.[9] Insulin resistance (IR) is the main feature of metabolic syndrome, and is characterised by hyper-insulinaemia in patients with normal fasting glucose. It has been associated with increased risk of developing diabetes mellitus (T2DM), cardiovascular disease and non-alcoholic fatty liver disease.[10] Accumulating large body of literature, including molecular, pathological, epidemiological, randomised controlled trials and observational studies, has highlighted the interaction between HCV and glucose metabolism (IR/T2DM).[11–16] Although earlier works referred to that, a higher baseline homeostasis model assessment of insulin resistance (HOMA-IR) score predicted a poorer SVR rate to Peg-IFN-α/ribavirin in treatment-naïve chronic hepatitis C patients[8, 17–20]; these data were not universally confirmed by all studies.[21] In the view of the suboptimal response to the current standard in therapy; this postulated correlation between IR and SVR has gained a great importance, as one of the modifiable risk factor. Therefore, we performed a systematic review and meta-analysis to evaluate, quantify and summarise the association between HOMA and SVR.

METHODS

Study selection criteria

Inclusion and exclusion criteria were defined prior to commencement of the literature search. Studies were included if they met the following criteria: they included treatment-naive HCV patients aged older than 18 years regardless of HCV genotype or the ethnic group; they provided information on SVR rates; and they were reported in the English language as full papers. Studies were excluded if they met the following criteria: they did not provide information on SVR; they did not allow correlation between the HOMA-IR and SVR; they included patients who were treated with nonpegylated interferons; they included patients with additional antivirals to Peg-IFN/RBV (e.g, amantadine); they included patients who were not treatment-naive; they included human immunodeficiency virus (HIV) co-infected patients; they included liver transplant recipients; letters/case reports, studies enrolling fewer than 10 subjects or articles not reporting outcomes of interest or primary data (editorials, reviews).

Literature search, study selection, and data extraction

We searched MEDLINE and EMBASE for studies published in the English language through December 2010 using a combination of the following terms: 'Hepatitis C'[Mesh] OR 'Hepacivirus'[Mesh] OR 'Hepatitis C, Chronic'[Mesh] AND 'Insulin resistance'[Mesh] OR 'Homeostasis Model of Assessment'[Mesh] AND 'Sustained virological Response'[Mesh]. Manual search of cited bibliographies was also performed. Only fully published articles were considered. Two researchers independently performed the literature search and data abstraction with regard to the inclusion and exclusion criteria by reading titles and abstracts. When reading titles and abstracts did not allow identification of eligible studies, articles were read in full. Relevant reviews and letters to the editor were excluded from the analysis, but read in full to identify potential relevant original studies. Disagreements between the two observers were resolved by discussion. Data from selected studies were extracted in a data sheet by MRG author and checked by a second author (ME). Disagreements could be resolved by discussion. The following data were extracted: year of publication, number of patients, cut-off of HOMA-IR to define IR, method of measurement of insulin, percentage of patients with normal insulin sensitivity and percentage of patients with advanced fibrosis.

End point

The main endpoint was the SVR rate, defined as the percentage of patients with undetectable HCVRNA (<50 IU/mL), 24 weeks after completion of therapy.

Statistical analysis

Statistical analysis was performed using the Meta-Disc software 1.4 (Zamora J, *et al.*, BMC Medical Research Methodology 2006, 6: 31.), considering: (i) a summary of data from individual studies, (ii) an investigation of the studies homogeneity graphical and statistically, (iii) calculation of clustered indexes and (iv) exploration of heterogeneity. Our assumption of heterogeneity was tested for each planned analysis using the Cochran-Q heterogeneity test. Random effects model using Der Simonian and Laird method was considered when heterogeneity was found. Only two-sided tests with a significance level of 0.05 were used. Confidence intervals (CIs) of individual studies were determined or approximated from the available data.

RESULTS

Seventeen eligible studies that fulfilled the inclusion and exclusion criteria are enrolled in the analysis,[8, 17–30] three studies without SVR rate according to baseline HOMA-IR were further excluded (Figure 1). The characteristics of these studies are shown in Table 1. Five studies were from Italy, three from Japan, two from Taiwan and one from Spain, United Kingdom, USA, France, India and Egypt. The used cut-off values for diagnosis of IR ranged from HOMA > 2 in 10 studies to HOMA > 2.5 in one study, HOMA > 2.7 in one study, HOMA > 3 in one study and HOMA > 3.5 in one study and was not available data in three studies. Nine studies found a statistically a significant association between HOMA-IR and SVR, and the other five studies did not find a significant association between HOMA-IR and SVR (Figure 2 and Table 1). Three of enrolled studies did not show SVR rate according to HOMA-IR. Thus, pooled data included 2129 patients in 14 studies. The meta-analysis including all 14 studies demonstrated that insulin resistance was associated with a remarkably lower likelihood of SVR, using random effects model by Der Simonian and Laird method, odds ratio was 2.86 (95%CI: 1.97–4.16) regardless of genotype (Figure 2). The test of heterogeneity (Cochran-Q = 36.92; df = 13; $P = 0.0004$) inconsistency $I^2 = 64.8\%$, and $\tau^2 = 0.287$. Sub-analysis including patients segregated by genotype 1, 2/3 or 4 demonstrated a negative and significant impact of increased HOMA-IR on SVR; three studies mixed genotypes were included and were separately analysed[17, 21, 29] (Table 2 and Figures 3–5). Even limiting the analysis to include only studies using cut-off HOMA > 2 for defining IR, the impact on SVR was maintained. Patients with HOMA-IR > 2 had significantly lower rates of SVR compared with patients with HOMA-IR < 2 (Figure 6), and this difference was largely independent of HCV genotype: HCV-1 (OR: 2.16; 95%CI: 1.51–3.08), HCV-2&3 (OR: 3.06; 95%CI: 1.06–8.82) and HCV-4 (OR: 6.65; 95%CI: 2.51–17.61). The difference in SVR rate in patients with IR compared with those with insulin sensitivity ranged from 3% to 41% in genotype 1, 5% to 57% in genotype 2/3 and 38% to 48% in genotype 4. The risk estimate for not achieving SVR from 10 studies using HOMA-IR > 2 as cut-off value for diagnosis of IR was 3.1-fold. Simi-

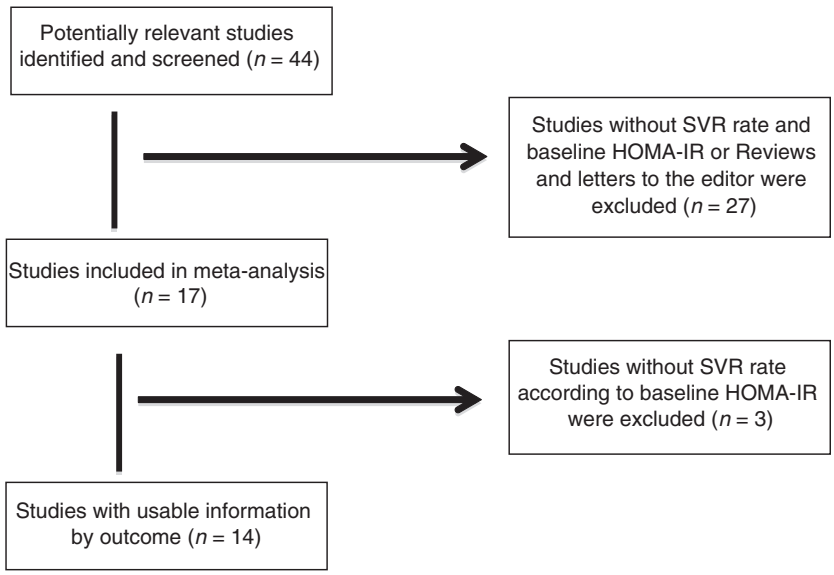

Figure 1 | Flow chart of studies screened and included in meta-analysis.

Table 1 | Studies included in meta-analysis addressing the impact of HOMA on sustained virological response

Author	Year	HOMA cut-off	SVR association	Insulin method	Mean HOMA-IR (s.d.)	% patients with IS	Genotype	*n*	SVR in IS	Non-SVR in IS	SVR in IR	Non-SVR in IR	Delta %SVR IS–IR	OR (95%CI)
Akuta *et al.*	2009	3.5	No	NA	2.6 (2.6)	0.28	1	123	11	9	26	26	0.05	0.82 (0.29–2.33)
Bortoletto *et al.*	2010	3	Yes	EIA	1.9 (1.1)	0.61	1	36	8	14	2	12	0.22	0.29 (0.051–1.49)
Camma *et al.**	2006	NA	No	NA	2.65 (2.01)		1	291	NA	NA	NA	NA		NA
Chu *et al.*	2008	2	Yes	EIA	2.93 (0.14)	0.31	1	133	38	3	50	42	0.38	0.14 (0.005–0.54)
Conjeevaram *et al.*	2007	2	Yes	NA	3.5 (5.0)	0.33	1	399	65	68	96	170	0.13	0.87 (0.77–0.99)
Dai *et al.*	2009	2.5	Yes	RIA	2.24 (2.46)	0.71	1	150	75	31	22	22	0.21	0.87 (0.75–0.97)
Fattovich *et al.*	2010	2	No	ECLIA	2.7 (2.5)	0.44	1	181	37	43	44	57	0.03	0.9 (0.5–1.64)
Grasso *et al.*	2009	2	No	EIA	2.6 (2.1)	0.77	1	90	34	35	8	13	0.11	0.63 (0.23–1.72)
Miyaaki *et al.*	2009	2	No	NA	1.9 (0.87)	0.51	1	39	11	9	6	13	0.23	0.37 (0.1–1.38)
Mizuta *et al.*	2010	2	Yes	NA	1.92 (1.92)	0.51	1	51	17	9	6	19	0.41	0.17 (0.049–0.57)
Petta *et al.*	2009	2.7	No	EIA	2.73 (1.69)	0.65	1	83	32	22	14	15	0.11	0.64 (0.17–3.03)
Romero-Gomez *et al.*	2005	2	Yes	ECLIA	3.01 (2.67)	0.38	1	113	26	17	23	47	0.28	0.55 (0.33–0.93)
Walsh *et al.**	2006	NA	No	NA	2.02 (0.19)		1	66	NA	NA	NA	NA		NA
Bortoletto *et al.*	2010	3	Yes	EIA	1.9 (1.1)	0.67	2&3	21	14	0	3	4	0.57	NC
Dai *et al.*	2009	2.5	No	RIA	2.24 (2.46)	0.71	2&3	180	117	11	44	8	0.07	0.87 (0.75–0.97)
Fattovich *et al.*	2010	2	No	ECLIA	2.7 (2.5)	0.57	2&3	209	93	26	66	24	0.05	0.8 (0.42–1.54)
Poustchi *et al.*	2008	2	Yes	RIA	3.34 (3.34)	0.41	2&3	82	32	2	31	17	0.30	0.15 (0.03–0.77)
Walsh *et al.**	2006	NA	No	NA	2.02 (0.19)		2&3	79	NA	NA	NA	NA		NA
Khattab *et al.*	2010	2	Yes	ECLIA	2.82 (1.19)	0.40	4	131	47	6	32	46	0.48	0.07 (0.01–0.43)
Moucari *et al.*	2009	2	Yes	ECLIA	3.7 (4.0)	0.49	4	108	39	20	14	35	0.38	0.19 (0.07–0.51)
								2565						

.HOMA, Homeostasis Model of Assessment; SVR, sustained virological response; OR, odds ratio; IS, insulin sensitivity (HOMA under cut-off); IR, insulin resistance (HOMA above cut-off); NA, non-available; ECLIA, electrochemiluminescence immunoassay; EIA, enzyme immunoassay; RIA, radio immunoassay; NC, calculation not allowed.

* Not included in meta-analysis due to lack of data.

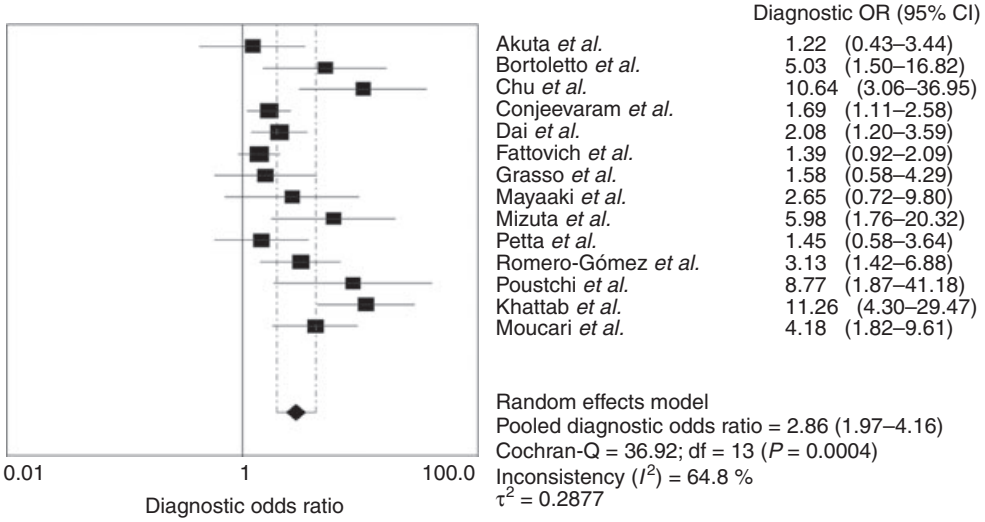

Figure 2 | Odd ratios and 95% CI for the association between insulin resistances assessed by HOMA-IR and sustained virological response to antiviral therapy in chronic hepatitis C patients treated with interferon + ribavirin in 14 studies. Black boxes indicate point estimates for OR.

Table 2 | Random effect model for pooled data according to genotypes

Genotype	Studies number	Pooled data OR (95%CI)	Heterogeneity (Cochran-Q)	Inconsistency, I^2 (%)
All	14	0.35 (0.24-0.51)	36.92, P = 0.0004	64.8
Genotype 1	11	0.46 (0.32-0.66)	18.05, P = 0.05	44.6
Genotype 2&3	4	0.33 (0.11-0.94)	8.78, P = 0.03	65.8
Genotype 4	2	0.15 (0.05-0.40)	2.35, P = 0.12	57.4
HOMA cut-off 2	10	0.33 (0.20-0.53)	35.9, P = 0.0001	72.1

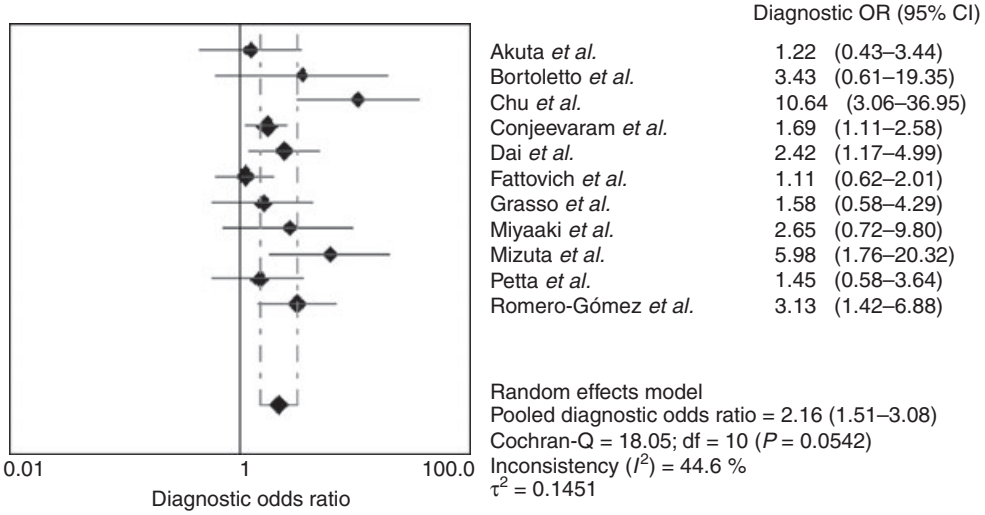

Figure 3 | Odd ratios and 95% CI for the association between insulin resistances assessed by HOMA-IR and sustained virological response to antiviral therapy in genotype 1 chronic hepatitis C patients treated with interferon + ribavirin in 11 studies. Black boxes indicate point estimates for OR.

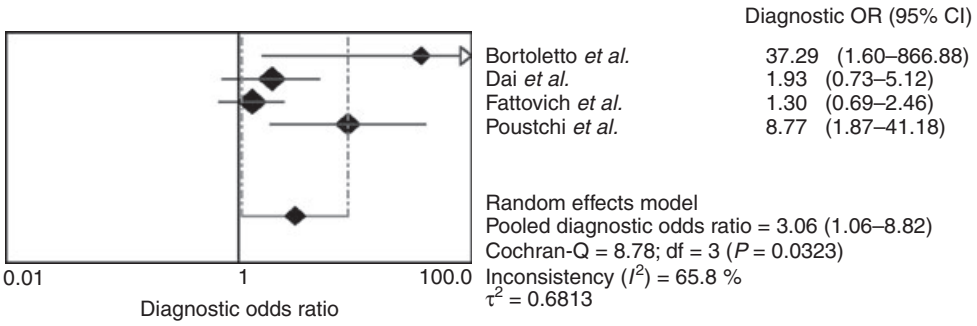

Figure 4 | Odd ratios and 95% CI for the association between insulin resistances assessed by HOMA-IR and sustained virological response to antiviral therapy in genotype 2 and 3 chronic hepatitis C patients treated with interferon + ribavirin in four studies. Black boxes indicate point estimates for OR.

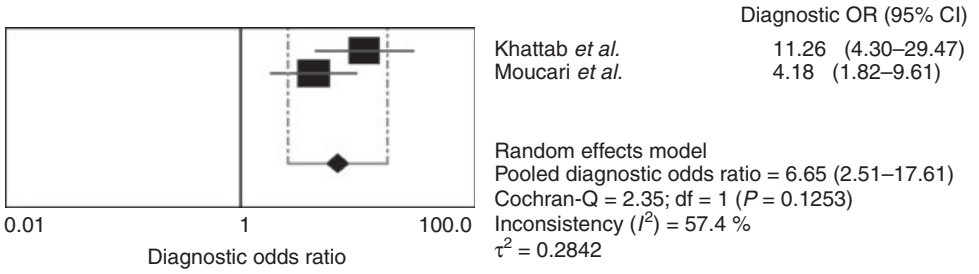

Figure 5 | Odd ratios and 95% CI for the association between insulin resistances assessed by HOMA-IR and sustained virological response to antiviral therapy in genotype 4 chronic hepatitis C patients treated with interferon + ribavirin in two studies. Black boxes indicate point estimates for OR.

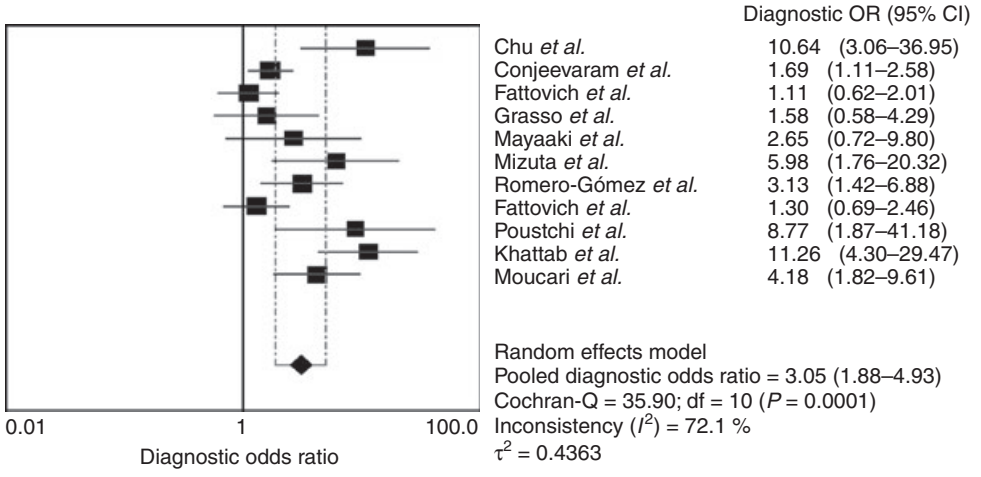

Figure 6 | Odd ratios and 95% CI for the association between insulin resistances assessed by HOMA-IR and sustained virological response to antiviral therapy in chronic hepatitis C patients treated with interferon + ribavirin in 10 studies using HOMA-IR > 2 as cut-off defining insulin resistance. Black boxes indicate point estimates for OR.

larly, the pooled estimates from 11 studies enrolled patients infected with HCV genotype 1 indicate a statistically significant 2.16-fold decrease in the incidence of SVR among patients with IR. Some studies that found no association were characterized by including cohorts of patients with a mean HOMA-IR < 3 and without

advanced fibrosis. In these studies, multivariate analysis demonstrated independent variables associated with SVR strongly related to metabolic abnormalities showing a tight co-linearity with HOMA-IR like body mass index, steatosis, elevated γ-glutamyl-transpeptidase (GGT), age and fibrosis.

DISCUSSION

This meta-analysis of published studies indicates that IR assessed by HOMA-IR is associated with an approximately threefold increase in risk of failure to achieve SVR to Peg-IFN/RBV in treatment naive patients with hepatitis C regardless of viral genotype. The discrepancy between the results of the cohorts in this review may be refereed to fact that the interaction between IR and SVR is very complex and depends on numerous factors that need to be considered when interpreting the data: (i) measurement and interpretation of HOMA-IR; (ii) colinearity between HOMA-IR and variables associated with metabolic derangements; and (iii) the characteristics of the cohort under study. First HOMA-IR, which was developed by Matthews *et al.*[31] as an indirect surrogate marker of IR was hampered by many concerns, which may influence the extracted data. These factors includes: methods of measurement of insulin, handling of blood samples, the conversion factor between SI units and mU/mL, the formula to calculate HOMA-IR and the threshold to define IR. For example: (i) Insulin assays are not standardised and are not comparable between studies. Insulin inter-assay variations can be large, and values have varied considerably between different laboratories.[32, 33] (ii) Careful handling of the blood samples is essential because haemolysis results in the degradation of insulin, whereas freezing the samples results in the degradation of C-peptide and glucose, with false-negative results being one of the consequences. (iii) Insulin should be reported in International Units (SI), but the conversion factor from microUnits/mL to SI units is not uniform among manufacturers; values ranging between 6 and 7.15 with no real scientific justification.[34] (iv) HOMA-IR could be calculated using the formula from Matthews *et al.* or using the HOMA-2 calculator (available at http://www.dtu.ox.ac.uk/homacalculator/). However, results from both methods are quite different and could bias the final analysis in comparative studies. (v) As insulin secretion is pulsatile, the use of a single fasting blood sample to diagnose IR in CHC, although convenient, potentially underestimates the prevalence and degree of this disturbance. The mean value from three samples taken at 5-min intervals to compute HOMA is, theoretically, better than a single sample determination.[22] However, in practice, a single sample is often taken and, if population estimators are found, this is an acceptable compromise that yields a similar result for large datasets. No evidence is available in setting of CHC patients. (vi) Ultimately, till now, there is no international consensus regarding the threshold that defines IR using HOMA-IR. Recently, Lam *et al.* showed that HOMA-IR > 4 was the optimal value defining IR in hepatitis C setting when compared with steady-state plasma glucose.[35]

However, these data need to be further confirmed in different populations, using euglycaemic hyperinsulinaemic clamp as gold-standard, and taking ethnicity and obesity into account when evaluating changes in HOMA-IR over time.[26] Second, HOMA-IR shows a strong colinearity with several variables implicated in metabolic disturbances such as obesity, hepatocyte steatosis, elevated GGT, fibrosis and older age. All these variables provide information, at least in part, on the metabolic abnormalities occurring in the individual, the final outcome of the multivariate analysis depending on the interactions between them. Interestingly, in our review to the negative studies that failed to find an association between IR and SVR; the mean baseline HOMA-IR was <3 in all studies, and the prevalence of advanced fibrosis or cirrhosis was also lower or even these studies had excluded cirrhosis or had been under-powered. This observation supporting the idea that the more difficult-to-treat cohort, the better the HOMA-IR prediction. In one of the negative studies, when HOMA-IR was excluded from the multivariate model, one of these variables emerged as independently associated with SVR. This highlights that this type of statistical bias is very difficult to resolve when strongly related variables were included in the analysis. Indeed, Dai *et al.*[17] demonstrated that the association of HOMAIR with SVR was stronger in cohorts including very difficult-to-treat patients. Ultimately, when more sophisticated methods to measure IR (such as whole-body insulin sensitivity) were used, a stronger association was reported between IR and SVR.[28] Thirdly, several viral and host factors have an impact on response to treatment,[36, 37] and these factors may influence the final outcome and explain the difference of results of these cohorts. Further study is needed to clarify the interaction of genotype, the degree of IR, gender and genetics (such as the IL28β mutation) and viral kinetics.

This meta-analysis has undoubtedly some limitations, as there is heterogeneity in the enrolled studies including characteristics cohort, methods for insulin measurement

and HOMA-IR interpretation that may have influenced on the concluded results.

In conclusion, this meta-analysis provides evidence that impaired HOMA-IR was associated with a lower cure rate of patients with hepatitis C treated with Peg-IFN/RBV. The differences are greater in cohorts of patients who are difficult to cure (higher insulin resistance, higher prevalence of advanced fibrosis). The inherent limitations in the determination and calculation of HOMA-IR may explain, at least in part, the variability detected in the results. Better handling and interpretation of HOMA are mandatory until the development of new tools for assessment of insulin resistance.

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