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Correlation of interferon-lambda 4 ss469415590 with the hepatitis C virus treatment response and its comparison with interleukin 28b polymorphisms in predicting a sustained virological response: a meta-analysis

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SUMMARY

Background: Interferon-lambda 4 (IFNL4) ss469415590 is a newly discovered polymorphism that could predict the treatment response in hepatitis C virus (HCV)-infected patients. This meta-analysis was performed in order to clarify its specific effect on the treatment response and to compare it with interleukin 28b (IL28B).
Method: The commonly used literature databases were searched. Meta-analyses were performed with fixed/random-effects models using Stata 12.0. The sustained virological response (SVR) rate was summarized using R software. Publication bias was examined through Egger's test.
Results: A total of seven studies were finally included in this meta-analysis. IFNL4 ss469415590 was demonstrated to be associated with SVR (odds ratio (OR) 3.83, 95% confidence interval (CI) 3.22–4.56, $p < 0.001$). Asians had a higher likelihood of achieving SVR than Caucasians (OR = 7.36 vs. 3.54). When stratifying all the patients according to HCV genotype, a significant association was observed in HCV genotype 1 patients (OR 4.5, 95% CI 2.91–6.95, $p < 0.001$). In HCV genotype 2/3 patients, the favorable TT/TT genotype patients tended to have a statistically higher SVR rate than the non-TT/TT genotype patients (84.4% vs. 78.3%, $p = 0.058$). Compared with IL28B rs12979860 (OR 3.45) and rs8099917 (OR 3.50), ss469415590 TT/TT genotype patients showed a slightly higher probability of achieving a SVR (OR 3.61 calculated from studies investigating both IFNL4 and rs12979860; OR 4.86 for studies investigating both IFNL4 and rs8099917). Furthermore, ss469415590 showed a slightly higher predictive value than rs12979860 using the diagnostic test tool (area under the curve = 0.71 vs. 0.70). IFNL4 was also correlated with rapid virological response (RVR) (OR 4.35, 95% CI 1.43–13.20, $p = 0.01$), viral clearance (OR 0.31, 95% CI 0.24–0.39, $p < 0.001$), and HCV susceptibility (OR 0.76, 95% CI 0.65–0.89, $p = 0.001$).
Conclusions: IFNL4 ss469415590 is significantly associated with SVR in HCV genotype 1 patients, irrespective of race; there is a tendency towards an association in HCV genotype 2/3 patients. Comparable to IL28B, IFNL4 is correlated with natural viral clearance and HCV susceptibility, additionally IFNL4 ss469415590 has a slightly higher predictive performance over IL28B polymorphisms in regard to SVR.

1. Introduction

Hepatitis C virus (HCV) is one of the main causes of chronic hepatitis and it affects around 3% of the world population.[1] Following acute HCV infection, as many as 80% of infected patients fail to eradicate the virus spontaneously; these patients then develop a chronic infection, which may progress to cirrhosis or even hepatocellular carcinoma (HCC).[2]

Pegylated-interferon (PEG-IFN) plus ribavirin (RBV) is currently one of the treatment regimens for chronic hepatitis C patients. It has been reported that the treatment efficacy might be influenced by virus- and host-related factors.[3] Previous studies have explicitly demonstrated that interleukin 28b (IL28B) polymorphisms have an influential impact on the HCV treatment response, such as the

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sustained virological response (SVR), rapid virological response (RVR), and spontaneous viral clearance.[4–6] Specifically, in patients infected with HCV genotype 1, those with the IL28B rs12979860 C allele or rs8099917 T allele have an almost two-fold increased likelihood of clearing the virus than those with the T allele or G allele, respectively. This effect has since been extended to genotype 2/3 and even genotype 4 patients.[7–9]

The mechanism by which IL28B influences the treatment outcome remains elusive. One possible explanation is that IL28B, a type of interferon (IFN-lambda), not only induces antiviral activity by itself, but also elicits IFN-stimulated genes (ISGs), which also have antiviral activity against the virus.[10] Recently, Prokunina-Olsson et al. discovered a new dinucleotide variant ss469415590 (rs368234815) that is in disequilibrium linkage with rs12979860. The polymorphism ss469415590 leads to a frame shift mutation and thus creates a new gene designated as interferon-lambda 4 (IFNL4); this gene cannot be produced by homozygote individuals with the IFNL4 TT allele (IFNL4 TT/TT genotype).[6] A previously reported significant predictor for SVR–rs12979860–is actually located in the intron of IFNL4 and is known to be highly linked with IFNL4 ss469415590. In other words, it might be IFNL4 rather than IFNL3 that plays a decisive role in the response of HCV to treatment. Subsequently, Bibert et al. attested that ss469415590 TT/ΔG but not rs12979860 induces IL28B and interferon-gamma-inducible protein 10 (IP-10) expression, suggesting TT/ΔG as the sole functional variant temporarily.[11]

Since then, many more studies have focused on the association of IFNL4 polymorphism with the treatment response in HCV patients. Several studies have revealed that IFNL4 ss469415590 is correlated with SVR in genotype 1/4 patients, but not in genotype 2/3 patients.[11–13] Meanwhile, the probability of achieving a virological response has varied in different ethnicities, and ss469415590 is more strongly correlated with HCV clearance than rs12979860.[6,12,14,15] However, one study reported contradicting results showing that IFNL4 ss469415590 had no added benefit for SVR prediction compared to rs12979860,[16] and another study reported IFNL4 ss469415590 to show similar predicting performance to IL28B rs12979860.

Reliable evidence on IFNL4 polymorphism in regard to HCV susceptibility, virus clearance, and the treatment response remains scarce, due in part to the different sample sizes and heterogeneity in HCV patients, treatment regimens, and durations of the medications used in the different studies. Furthermore, the influence of ss469415590 on the treatment response in HCV-2 and HCV-3 patients has been less convincing. Therefore, a meta-analysis was performed in the present study to comprehensively appraise the influence of IFNL4 ss469415590 on the response to treatment and clearance of HCV, and to better clarify the effect of IFNL4 ss469415590 on the likelihood of achieving SVR and RVR in HCV patients. It was also attempted to estimate the predictive value of IFNL4 polymorphism for SVR in HCV patients receiving PEG-IFN/RBV and to compare IFNL4 and IL28B in regard to the predictive value.

2. Materials and methods

2.1. Search strategy

An electronic search was conducted to identify articles published up until September 13, 2015, in the following databases: PubMed, Web of Science, Chinese Biomedicine Database, and China National Knowledge Infrastructure (CNKI). Medical subject heading (MeSH) terms were the priority in setting the strategy. The following keywords were used: "IFNL4", "interferon-lamda 4" , "interferon lambda 4", "interferon-λ4" or "IFN-λ4" or "ss469415590" or "rs368234815". In addition, the references listed in the articles included were screened so as not to miss any additional eligible studies.

2.2. Criteria for article screening

Studies were included if they met the following criteria: (1) the article assessed the association between IFNL4 polymorphisms and the HCV treatment response or susceptibility; (2) the treatment response included SVR and/or RVR; (3) the study design was a case–control study or cohort study; (4) the odds ratio (OR) with the 95% confidence interval (95% CI) was reported, or could be calculated using the data available. Unpublished reports such as conference abstracts were not included. Articles including patients with hepatitis B virus (HBV) or HIV co-infection were all excluded. In the case of more than one study being performed by the same author(s), these were regarded as independent studies if the two inclusion time periods did not overlap.

2.3. Data collection

The data were extracted independently by two investigators (YL and LY). In the case of any disagreement, the other investigators were consulted until a consensus was reached. The following information was extracted: first author's name, date of publication, ethnicity, country, number of patients, treatment regimen, duration of treatment, mean age, proportion of male patients, and IFNL4 single nucleotide polymorphism (SNP) genotype distributions.

2.4. Treatment outcome

The primary treatment outcome of this meta-analysis was SVR after treatment with PEG-IFN plus RBV, which was defined as undetectable HCV RNA at 24 weeks after the cessation of treatment. The secondary treatment outcome was RVR, which was defined as the eradication of serum HCV RNA at week 4 after the initiation of PEG-IFN plus RBV.

2.5. Quality assessment

The quality of the studies included in this meta-analysis was appraised using previously reported tools.[17,18] An eight-point scoring system was created based on details of the clinical characteristics reported (**Supplementary Material**, Table S1); a score of less than 6 points was deemed to indicate a low quality study.

2.6. Statistical analysis

Correlation of IFNL4 polymorphisms with the HCV treatment response was estimated through the summary OR and corresponding 95% CI. The overall effect was assessed using the *Z*-test; results were considered significant if the *p*-value was less than 0.05. The heterogeneity of the included articles was evaluated using I^2 statistics (heterogeneity was accepted if $p > 0.1$ and $I^2 \leq 50\%$). If the value of the I^2 statistic is less than 50% or the *p*-value is more than 0.1, the fixed-effects model can be used; otherwise, a random-effects model should be used. Egger's test was performed to examine publication bias. When estimating the OR, the dominant model (AA: AB + BB, A as the major allele, B as the minor allele) and the allele model (A vs. B) were used. The overall rate of SVR was calculated in a way that resembles meta-analysis: each study is conferred a weight, and the SVR rate of each study is adjusted according to the weight that the study contributes to the overall SVR rate.

All of the statistical analyses were performed using Stata (version 12.0) or R (version 3.0.1) software. All tests were two-sided and $p < 0.05$ was regarded as statistically significant.

3. Results

A flow diagram depicting the screening process, modified according to the PRISMA statement, is given in Figure 1.[19] After reading the titles and abstracts, 20 articles were included for full-text review. Among these, no treatment was involved in three articles,[20–22] the data were not accessible for two articles,[23,24] SVR was not included clearly as the treatment outcome in three articles,[25–27] one article reported the treatment response in liver recipients after transplantation,[28] and one article included HCV/HIV co-infected patients.[29] Additionally, five studies were conducted by the same group;[14,15,30–32] therefore the most recent two were selected (Nagaoki[31] and Ochi[14]); one of these provided detailed genotype information and one presented detailed allele frequencies. After excluding these 13 studies, the remaining seven articles were included in the meta-analysis, among which six articles investigated SVR,[6,11–13,16,31] three articles investigated RVR,[13,16,31] one study investigated susceptibility,[14] and two studies explored spontaneous clearance.[6,11] These articles included a total 4480 HCV patients. The quality assessment showed that only one study scored less than 6 points and was thus categorized as a low quality study.[31] All of the other studies were of high quality (**Supplementary Material**, Table S1). The characteristics of the qualifying articles are summarized in Table 1.

3.1. IFNL4 polymorphisms and the treatment response in HCV patients

In this meta-analysis, six studies provided detailed information on genotyping and one article provided only the allele frequency[14] in the analysis of the association of IFNL4 polymorphism with SVR. Among the six studies, 3577 patients were enrolled, including 1705 patients who achieved SVR and 1872 patients who had no SVR. The favorable IFNL4 genotype (TT/TT) was present in 34.4% of the 3577 patients. Overall, 65.9% (95% CI 52.9–78.9%) of the TT/TT genotype patients achieved SVR compared to 36.4% (95% CI 22.8–50.1%) of the non-TT/TT genotype patients. Asian HCV patients who had the TT/TT genotype had a higher SVR rate (88.4%, 95% CI 79.8–97.0%) than Caucasian patients (58.4%, 95% CI 42.3–74.6%) (Table 2).

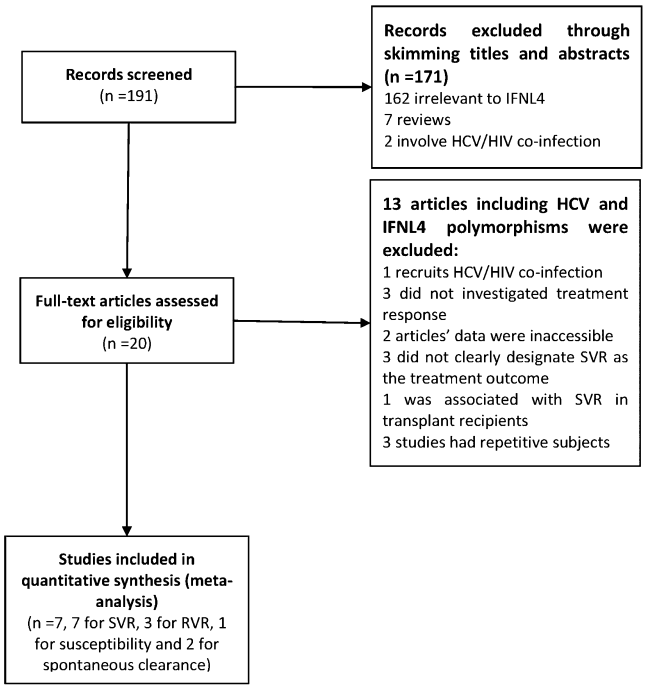

Figure 1. Flow chart of the article screening process for the meta-analysis.

Meanwhile, the TT/TT genotype correlated with a 3.83-fold increased probability of achieving SVR (95% CI 3.22–4.56, $p < 0.001$); moderate heterogeneity existed ($I^2 = 28.8\%$, $p_{hetero} = 0.188$) (Table 3, Figure 2A). On subgroup analysis according to ethnicity, heterogeneity diminished for each race. Results showed that Asians were more likely to achieve SVR than Caucasians (Asian, OR 7.36, 95% CI 4.41–12.28, $p < 0.001$; Caucasian, OR 3.54, 95% CI 2.94–4.26, $p < 0.001$).

In the allele model, allele TT still favored SVR (OR 2.23, 95% CI 2.00–2.48, $p < 0.001$) (Table 3, Figure 2B). Asian patients who carried the TT allele still had a higher probability of achieving SVR compared to Caucasian patients with the TT allele (Asian, OR 3.39, 95% CI 2.51–4.56, $p < 0.001$; Caucasian, OR 2.09, 95% CI 1.86–2.43, $p < 0.001$), which is consistent with the aforementioned results (Table 3).

Next a subgroup analysis was conducted based on HCV genotype. Five studies investigated HCV genotype

Table 1
Clinical characteristics of the studies included in this meta-analysis

First author	Year	Race	Country	Patient trait	Inclusion time	Treatment regime	Duration of treatment	Genotyping method	SVR/NR, *n*/*n*
Stattermayer et al.[12]	2014	Caucasian	Austria	Treatment-naïve	2001–2011	PEG-IFN + RBV	GT1/4: 24–72 weeks; GT2/3: 24 weeks	RT-PCR + TaqMan	475/279
Ochi et al.[14]	2014	Asian	Japan	NA	–	PEG-IFN-α-2b + RBV	48 weeks	Multiplex PCR followed by the Invader assay	547/356
Nagaoki et al.[31]	2014	Asian	Japan	NA	–	PEG-IFN-α-2b + RBV + TVR for 12 weeks, PEG-IFN-α-2b and RBV an additional 12 weeks	24 weeks	Invader assay	226/57
Akkarathamrongsin et al.[13]	2014	Asian	Thai	NA	2007–2012	PEG-IFN-α-2a/2b + RBV	GT1: 48 weeks; GT3: 24 weeks	TaqMan genotyping	177/48
Prokunina-Olsson et al.[6]	2013	Caucasian	USA	NA	–	PEG-IFN-α-2b + RBV	48 weeks	TaqMan genotyping	286/950
Bibert et al.[11]	2013	Caucasian	Switzerland	NA	2001–2013	PEG-IFN-α-2b + RBV	48 weeks	TaqMan	337/203
Palmieri et al.[16]	2014	Caucasian	Italy	Treatment-naïve	2005–2010	PEG-IFN-α-2b or α-2a + RBV	48 weeks	TaqMan	204/335

SVR, sustained virological response; NR, non-response; PEG-IFN, pegylated interferon; RBV, ribavirin; GT, genotype; PCR, polymerase chain reaction; NA, not available; TVR, telaprevir.

Table 2
Virological response rate in patients carrying different IFNL4 genotypes

SNPs	Number of articles included	VR/NR	Total response rate (95% CI)	Response rate in TT/TT genotype (95% CI)	Response rate in non-TT/TT genotypes (95% CI)
IFNL4					
SVR	6	1705/1872	47.4% (29.6–65.3%)	65.9% (52.9–78.9%)	36.4% (22.8–50.1%)
Race					
Asian	2	403/105	79.3% (75.8–82.9%)	88.4% (79.8–97.0%)	56.5% (48.3–64.7%)
Caucasian	4	1302/1767	41.6% (22.4–60.8%)	58.4% (42.3–74.6%)	31.8% (16.9–46.8%)
Genotype					
GT1	5	869/805	53.9% (37.8–69.9%)	73.7% (61.9–85.4%)	38.8% (28.7–48.9%)
GT2/3	3	466/108	81.0% (77.7–84.2%)	84.4% (80.3–88.6%)	78.3% (73.5–83.1%)
RVR	3	489/558	55.6% (18.7–92.6%)	68.9% (53.9–83.9%)	36.5% (0–74.6%)

IFNL4, interferon-lambda 4; SNP, single nucleotide polymorphism; VR, virological response; NR, no response; CI, confidence interval; SVR, sustained virological response; RVR, rapid virological response.

1 patients.[6,12,13,16,31] Genotype 1 patients who carried the TT allele had a higher SVR rate (73.7%, 95% CI 61.9–85.4%) than non-TT allele carriers (38.8%, 95% CI 28.7–48.9%) (Table 2). The probability increased to 4.5-fold (95% CI 2.91–6.95, $p < 0.001$), which is higher than the overall effect (OR 3.83) in HCV patients (Table 3; **Supplementary Material**, Figure S1). Also, in Asian HCV-1 patients, the probability of achieving SVR was higher than that in Caucasian HCV-1 patients (OR 9.79 vs. 4.3, respectively).

For genotype 2/3 patients, three studies including 486 SVR patients and 108 non-SVR patients were assessed. The results indicated an insignificant predictive role of IFNL4 TT/TT genotype for SVR in genotype 2/3 patients (OR 1.43, 95% CI 0.91–2.26, $p = 0.125$) (Table 3; **Supplementary Material** Figure S2) in these studies.

When analyzing the SVR rate in TT/TT genotype and non-TT/TT genotype patients, around 84.4% (95% CI 80.3–88.5%) of TT/TT patients and 78.3% (95% CI 73.5–83.1%) of non-TT/TT patients achieved SVR ($p = 0.058$) (Table 2). Additionally, IFNL4 ss469415590 TT/TT genotype was associated with HCV genotype 4 (OR 8.53, 95% CI 3.00–24.26, $p < 0.001$) and genotype 6 patients (OR 7.08, 95% CI 2.87–17.45, $p < 0.001$) (Table 3).

Among all the studies included, three focused on RVR.[13,16,31] In total, 489 patients who had RVR and 558 patients who did not were included. The results indicated that the IFNL4 TT/TT genotype was correlated with a 4.35-fold increased likelihood of achieving RVR (95% CI 1.43–13.20, $p < 0.001$) (Table 3) compared with the non-TT/TT genotype when both received IFN plus RBV.

3.2. IFNL4 polymorphisms and HCV susceptibility and spontaneous clearance

After Prokunina-Olsson et al. reported IFNL4 to be associated with impaired clearance of HCV,[6] several studies replicated this experiment. Confirmation was obtained that the IFNL4 TT/TT genotype favored spontaneous clearance (OR 0.31, 95% CI 0.24–0.39, $p < 0.001$). Additionally, one study recruited healthy controls.[14] The results showed that the IFNL4 TT/TT genotype has a protective effect on HCV chronic infection (OR 0.76, 95% CI 0.65–0.89, $p = 0.001$). The allele model again substantiated these conclusions (data not shown), which reinforced the association of IFNL4 polymorphisms with HCV susceptibility.

3.3. IL28B polymorphisms and the HCV treatment response in studies included in the meta-analysis

IL28B rs12979860 and rs8099917 were the main polymorphisms investigated in these studies. In total, five studies were included that concurrently focused on the relationship of IL28B rs12979860 with HCV, [6,11–13,16] and three studies investigated rs8099917.[12,16,31] Consistent with previous studies, rs12979860 and rs8099917 both correlated with SVR in the dominant model (rs12979860, OR 3.45, 95% CI 2.89–4.11, $p < 0.001$; rs8099917, OR 3.50, 95% CI 2.02–6.06, $p < 0.001$). Meanwhile, the overall effect of IFNL4 polymorphism on SVR was summarized based on the five studies that investigated rs12979860 and the three studies that investigated rs8099917. In the five studies analyzing rs12979860,

Table 3
Summary of the odds ratio and its 95% confidence interval in the meta-analysis

IFNL4	Number of studies	VR/NR	OR	95% CI	p-Value (OR)[a]	I^2	p-Value (Hetero)[b]	Effect model	Publication bias
SVR[c]	6	1705/1872	3.83	3.22–4.56	<0.001	28.80%	0.188	F	0.616
Asian	2	403/105	7.36	4.41–12.28	<0.001	0.00%	0.381	F	
Caucasian	4	1302/1767	3.54	2.95–4.26	<0.001	0.00%	0.665	F	
SVR (allele)	5	3698/4246	2.23	2.00–2.48	<0.001	37.00%	0.134	F	0.917
Asian	1	1094/712	3.39	2.51–4.56	<0.001	–	–	F	
Caucasian	4	2604/3534	2.09	1.86–2.34	<0.001	0	0.885	F	
Genotype[c]									
GT1	5	869/805	4.5	2.91–6.95	<0.001	61.30%	0.024	R	0.652
Asian	2	273/79	9.79	5.33–17.99	<0.001	0.00%	0.453	F	
Caucasian	3	596/726	3.69	2.81–4.84	<0.001	23.60%	0.27	F	
GT2/3	3	466/108	1.43	0.91–2.26	0.125	0	0.991	F	0.363
GT6	2	98/58	7.08	2.87–17.45	<0.001	0	0.333	F	–
GT4	1	65/49	8.53	3.00–24.26	<0.001	–	–	F	–
RVR[c]	3	489/558	4.35	1.43–13.20	0.01	90.40%	<0.001	R	0.918

IFNL4, interferon-lambda 4; VR, virological response; NR, no response; OR, odds ratio; CI, confidence interval; SVR, sustained virological response; F, fixed-effects model; R, random-effects model; GT, genotype; RVR, rapid virological response.

[a] Dominant model.

[c] p-Value for OR.

[b] p-Value for heterogeneity.

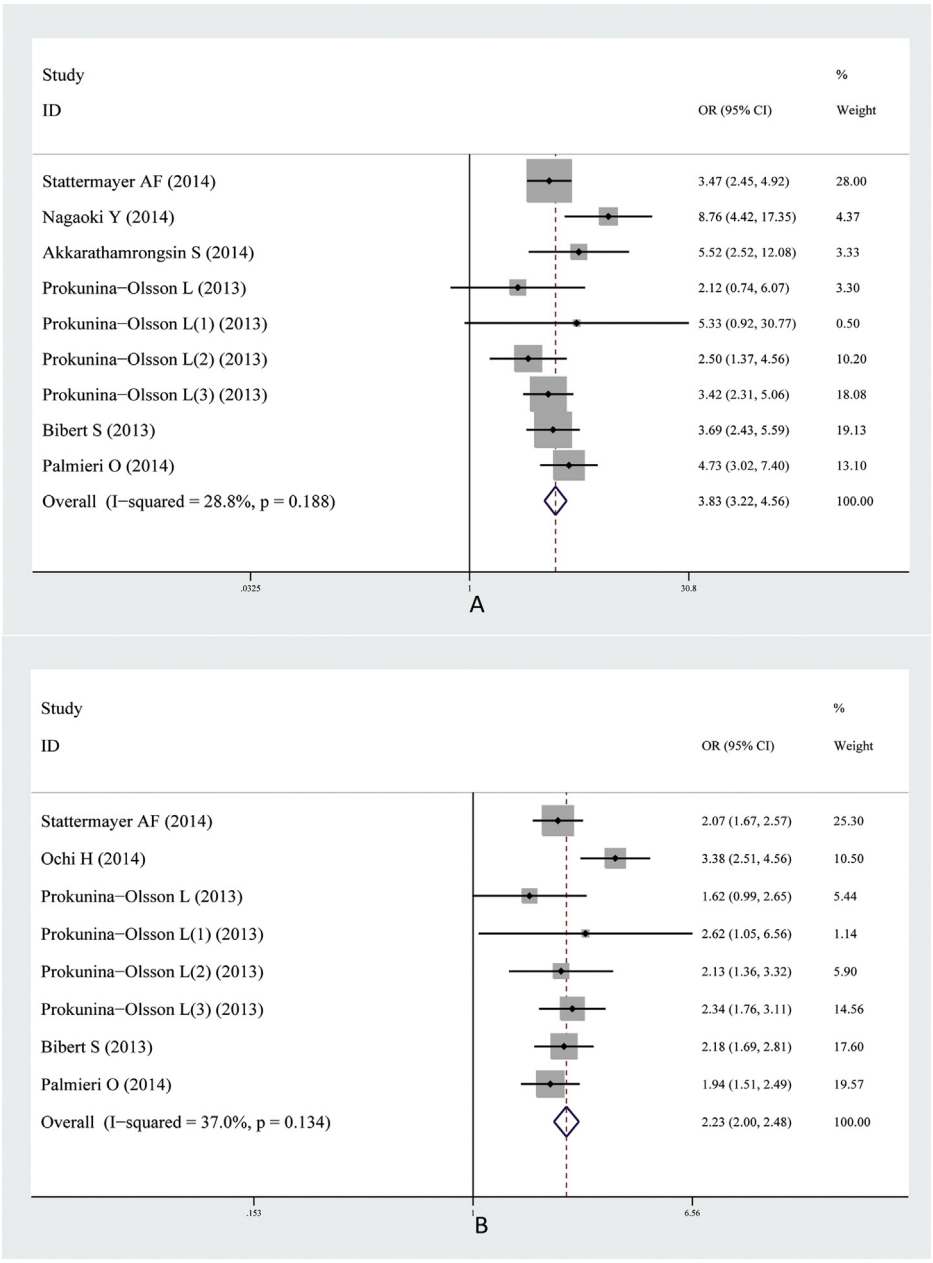

Figure 2. Forest plot for the overall odds ratio of IFNL4 with HCV SVR. (A) OR calculated in the dominant model; (B) OR calculated in the allele model. For the forest plot, the black diamond represents the OR estimate for each study and the size of the gray area reflects the weight in the pooled analysis; the horizontal line indicates the 95% confidence interval; the white diamond represents the pooled OR. (IFNL4, interferon-lambda 4; HCV, hepatitis C virus; SVR, sustained virological response.).

the OR of IFNL4 was 3.61 (95% CI 3.02–4.32, $p < 0.001$). In the three studies investigating rs8099917, the OR was 4.86 (95% CI 3.05–7.74, $p < 0.001$). Both ORs were higher than those for IL28B polymorphisms.

A diagnostic meta-analysis was then adopted to roughly evaluate the predictive values for SVR of IFNL4 ss469415590, rs12979860, and rs8099917. The clinical SVR diagnosis criteria were set as the gold standard reference. The case number of patients who carried the favorable genotype (TT/TT for ss469415590, CC for rs12979860, and TT for rs8099917) and finally achieved SVR was regarded as the true-positive value. By the same token, patients with the non-favorable genotype who achieved SVR were false-negative, patients with the favorable genotype who did not achieve SVR were false-positive, and patients with the non-favorable genotype who did not achieve SVR were true-negative. When the five studies that concurrently investigated IFNL4 and rs12979860 were analyzed, a slightly larger area under the curve (AUC) was obtained for IFNL4 ss469415590 (AUC 0.71, 95% CI 0.67–0.75) (**Supplementary Material**, Figure S3A) than rs12979860 (AUC 0.70, 95% CI 0.66–0.74) (**Supplementary Material**, Figure S3B). In the three studies that investigated both IFNL4 and rs8099917, the AUC could not be calculated as the number of studies was less than the number of quadrature points. However, the higher OR for the IFNL4 polymorphism indicated its higher performance in predicting SVR than IL28B.

3.4. Publication bias and sensitivity analysis

No publication bias was found for any of the studies included in this meta-analysis (Table 2; **Supplementary Material**, Figure S4), which is indicative of the accuracy of the overall effect summarized through meta-analysis.

A sensitivity analysis was conducted through the sequential omission of every study. After omitting each study, the overall effects of IFNL4 on the treatment response and spontaneous viral clearance did not differ significantly (data not shown). Therefore the results are reliable.

4. Discussion

In this study, it was clearly demonstrated that the IFNL4 ss469415590 (rs368234815) favorable genotype (TT/TT) was correlated with the HCV treatment response (SVR and RVR), especially in HCV-1 patients. In addition, IFNL4 polymorphism might also be associated with spontaneous virus clearance and chronic HCV susceptibility. Asians had a higher frequency of the TT/TT genotype than Caucasians, and thus had a higher probability of achieving SVR when both received standard treatment. IL28B rs12979860 and rs8099917 were still found to be correlated with SVR based on these studies, but seemed to have a weaker effect than IFNL4 ss469415590 in terms of the predictive value in SVR.

As described previously, IFNL4 ss469415590 has recently been discovered to be located upstream of IFNL3 (IL28B) and is in linkage disequilibrium with rs12979860.[6] Similar to IL28B, IFNL4 ss469415590 has a variable frequency distribution: Asians have a higher TT/TT genotype frequency than Caucasians. This in turn could reflect the SVR rate in the two different races, with Asians having a much higher rate than Caucasians. The present meta-analysis, which summarized the overall effect of IFNL4 in predicting SVR and also conducted a subgroup analysis based on race, substantiated this. Therefore, generally speaking, Asians who are chronically infected with HCV will have better outcomes.

Apart from the treatment response, IFNL4 polymorphism is also relevant to HCV susceptibility and natural virus clearance, which paralleled IL28B. Given the minor allele frequency distribution among the races and in light of the role of human leukocyte antigen DP/DQ (HLA-DP/DQ) in HBV, which is regarded as the main genetic factor that contributes to the discrepancy in prevalence worldwide,[33] it may also be concluded that IFNL4 or IL28B exerts such effects. With the higher favorable allele frequency of IFNL4 or IL28B in Asians, the prevalence of HCV in Asians is thus much lower than in the Caucasian population.

In spite of the similarities, disparity also exists between IFNL4 and IL28B. In this study, in addition to the overall effect of IFNL4 and IL28B calculated from the studies included, a comparison was made of the predictive effects of IFNL4 and IL28B based on the studies that concurrently investigated the two gene polymorphisms to eliminate the potential overestimation of the effects. By means of a diagnostic meta-analysis, it was clearly indicated that IFNL4 has a much stronger association with the treatment response and a higher predictive value for SVR, compared with IL28B rs12979860. Since the comparison was made in studies that simultaneously genotyped IFNL4 and IL28B polymorphisms, it was possible to keep the study population the same and to some extent eliminate some potential confounders, and the appraisal of the SVR predictive value was more persuasive. Additionally, in regard to disparity between IFNL4 and IL28B, some discordance in the genotypes might exist. In other words, some patients might have the IL28B rs12979860 major genotype but the IFNL4 minor genotype. Such patients might still achieve SVR and vice versa. These patients should be investigated in a future study to accurately analyze the relationship between IFNL4 and IL28B, which might be helpful in individualized treatment.

The subgroup analysis stratified by HCV genotype indicated that IFNL4 was definitely correlated with SVR in HCV-1 patients, with a higher likelihood of SVR in Asian HCV-1 TT/TT genotype patients than in Caucasian patients. However, from the few published studies that investigated HCV-2/3 patients separately, no beneficial effect in regard to SVR was observed in IFNL4 TT/TT genotype patients ($p > 0.05$). When the SVR rate was analyzed in TT/TT and non-TT/TT genotype patients, TT/TT patients showed an obviously higher SVR rate than non-TT/TT genotype patients (84.4% vs. 78.3%, $p = 0.058$). Therefore, the IFNL4 TT/TT genotype still tended to favor SVR in HCV-2/3 patients, although because of the limited number of studies, this effect did not reach statistical significance. Furthermore, several studies involving HCV-4 and even HCV-6 patients still indicated that the IFNL4 TT/TT genotype favored SVR in these two categories of patients. Thus, overall, the IFNL4 TT/TT genotype favored or at least showed a tendency to favor SVR for patients with each genotype of HCV.

Of note, another meta-analysis was published during the submission and revision of this paper.[33] Consistent with the present results, the authors of that meta-analysis showed that IFNL4 rs368234815 can predict SVR in HCV patients, which is independent of HCV genotype, patient ethnicity, and treatment regimen. A considerable number of studies have focused on this,[34,35] and the role of IFNL4 becomes more and more evident.

Although it was clearly found in this study that IFNL4 is correlated with the HCV treatment response, and it is also suggested that IFNL4 is slightly superior to IL28B in predicting SVR, the exact mechanism underlying these phenomena remains unclear. Bibert et al.[11] demonstrated that IFNL4 ss469415590 promotes the methylation of its adjacent cytosine residue, which remains unmethylated in TT/TT patients. They also showed that individuals carrying the mutant allele of IFNL4 express lower levels of IP-10, suggesting that IFNL4 exerts its effect through IP-10 and might be linked to some ISGs. However, the mechanism of this link is elusive and warrants exploration in further studies.

Certain other limitations should be stated with regard to this study. First, only two studies recruited Asian HCV patients (Japanese and Thai), thus whether the conclusions apply to patients in other Asian countries, such as China, Korea, etc., requires validation in further studies. Second, few studies focused on RVR, HCV susceptibility, and natural viral clearance, thus further subgroup analyses were not conducted since the statistical power would not have been sufficient after stratification. Third, when comparing the magnitude of the association between genetic factors and the disease state, it would be simpler and more direct to compare the p-values. However, the diagnostic meta-analysis was simulated in this study, and the predictive value for the favorable genotype of each SNP in SVR was compared. This would be more convincing than the single p-value in regard to appraising the performance of each SNP for predicting the probability of SVR; however, the AUC was not drawn for rs8099917 because of the limited number of studies (three studies). The OR of IFNL4 was still greater than that of rs8099917, therefore the conclusion could be drawn that IFNL4 excels in predicting SVR in HCV patients when receiving standard of care.

Notwithstanding these limitations, this meta-analysis comprehensively analyzed the overall effect of IFNL4 polymorphism ss469415590 on the HCV treatment response for the first time. It is concluded that the IFNL4 ss46941550 TT/TT genotype favors SVR and natural viral clearance, particularly in Asian patients as well as in HCV-1 patients. Compared with IL28B polymorphisms (rs12979860, rs8099917), IFNL4 ss469415590 might have a higher predictive value for SVR in HCV patients who have received previous standard of care. However, this study found only a negative association in HCV-2/3 patients, which might be attributable to the limited number of studies. Thus more studies investigating the relevance of IFNL4 with regard to SVR in HCV-2/3 patients are needed. Additionally, since the mechanism underlying the significant correlation of IFNL4 polymorphism with HCV SVR remains elusive, further studies should focus on this, which might provide evidence to help cure HCV infections in the future.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijid.2016.10.023.

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