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Effects of Interleukin-10 -1082G/A and -592C/A Gene Polymorphisms on the Risk of Human Immunodeficiency Virus-1 Infection: An Updated Meta-analysis

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ABSTRACT

This paper has aimed to review the available evidence on the association between Interleukin (IL) -10 -1082G/A, -592C/A gene polymorphisms and the risk of human immunodeficiency virus-1(HIV-1) infection. The data of PubMed updated in May 2021 were retrieved. The HIV infection risks were estimated in allelic, recessive, dominant, homozygous, heterozygous, over-dominant models of IL-10-1082G/A and-592C/A gene locus as odds ratio (*OR*) with the corresponding 95% confidence interval (95% *CI*). The correlation was not significant between -1082G/A polymorphism and HIV-1 susceptibility (allelic model (G vs. A: *OR* (95% *CI*)=0.968 (0.878-1.067)); recessive model (GG vs. AA+AG: *OR* (95% *CI*)=0.940, (0.771-1.146)); dominant model (GG+AG vs. AA: *OR* (95% *CI*)=0.967(0.846-1.106)); homozygous model (GG vs. AA: *OR* (95% *CI*)=0.971(0.780-1.209)); heterozygous model (AG vs. AA: *OR* (95% *CI*)=0.988(0.797-1.224)) and over-dominant model (GG+AA vs. AG: *OR* (95% *CI*)=0.969(0.781-1.201)). IL-10-592C/A polymorphism might be related to HIV-1 in allelic model, dominant model, homozygous model and heterozygous model (*OR* (95% *CI*)(0.796-0.965); *OR* (95% *CI*)=0.793(0.664-0.948); *OR* (95% *CI*)=0.755,(0.612-0.930); *OR* (95% *CI*)=0.820(0.679-0.991), respectively), but not to recessive model and over-dominant model (*OR* (95% *CI*)=0.882(0.770-1.010) and *OR* (95% *CI*)=1.009(0.897-1.148)).

Keywords: Interleukin-10, Polymorphism, HIV-1, Susceptibility, Meta-analysis

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INTRODUCTION

Since HIV infection was first discovered in 1981, it started to spread over the world and has become one of the most serious public health problems. In 2020, the World Health Organization announced that 37.7 million people live with HIV, 1.5 million new HIV infections, and 680 000 AIDS-related deaths. (https://www.who.int/news/item/01-12-2021-world-aids-day-2021---step-up-be-bold-end-aids-end-inequalities-and-end-pandemics). Finding effective prevention and treatment methods for HIV/AIDS has already become a key research direction globally. Some individuals get readily infected with HIV while some highly exposed individuals always remain uninfected (1-3), Kaur et al. found that genetic variants might regulate HIV-1 susceptibility (4). Previous studies have identified 14 AIDS restriction genes, polymorphic variants that could regulate disease prevention and progression (5), suggesting that IL-10 genes might be a key part in susceptibility to and progression of HIV-1 infection.

Interleukin (IL)-10 is a kind of multifunctional cytokine largely secreted by immunocytes, such as monocytes, macrophages, T helper 2 cells , and B cells, and it plays a significant role in regulating immune responses (6, 7). IL-10 gene, located on chromosome 1q31–32, has three measurable single nucleotide polymorphisms (SNPs)—-1082 G to A (rs1800896), -592 C to A (rs1800872) and-819 C to T (rs1800871)—in its proximal promoter region (8), which determines its production (9, 10). Many studies have demonstrated that IL-10 plays a certain role in attenuating the decrease of CD4 count and in inhibiting immune activation steps by presenting antigen, activating macrophage, producing cytokine, , proliferating antigen-specific T cells as well as the viral replication (11). The level of IL-10 is different in serum HIV-1 antibody positive and negative patients and at different stages of AIDS (12). Given the above-mentioned functions of IL-10, these promoter polymorphisms were supposed to be potential factors for susceptibility to HIV-1 infection.

Up to now, several studies have already indicated that IL-10 gene polymorphisms are related to HIV infection, however, the conclusions were not consistent, even contradictory. A previous meta-analysis reported that -529C/A gene polymorphism might reduce HIV-1 infection risk (13), nonetheless, the study's sample size was a little modest. (12, 14-20). Therefore, this study updated this meta-analysis by summarizing a large number of studies to analyze the relationship between IL-10 gene promoter polymorphisms and HIV susceptibility.

METHODS AND MATERIALS

Literature Retrieval Strategy

The pieces of literature were systematically searched from PubMed up to May 2021. The database was searched up with various combinations of the following keywords: "interleukin-10", "Interleukin 10", "IL10", "IL-10", "HIV", "AIDS", "HIV-positive", "human immunodeficiency virus", "acquired immune deficiency syndrome", "human immunodeficiency virus-positive", "polymorphism", "polymorphisms", "mutation", "allele", "genotype", "genetic variant" and "genetic". Furthermore, we inquired whether there were any additional potentially relevant papers assessed from the included research and reviews' follow-up references.

Inclusion and Exclusion Criteria

Eligible studies met the following four inclusion criteria: (a) case-control or cohort study; (b) relevant to the association between IL-10 gene polymorphisms and HIV-1 susceptibility; (c) available data on allele frequencies or genotype distributions; (d) enough data to calculate odds ratio (*OR*) and their 95% confidence interval (95% *CI*).

The excluded studies were (1) repeated

or overlapped publications; (2) reviews or abstracts; (3) no frequencies of genotype.

Data Extraction

Two investigators had to independently extract information from all the qualifying articles. . The following information had to be concluded: author, public year, country, ethnicity, numbers of case and control, as well as allele and genotype distributions information. Arguments associated with data harvesting had to be resolved via consultation by the review committee.

Statistical Analysis

The crude *ORs* with their 95% *CI* were used to measure the impact of IL-10 gene polymorphisms on HIV-1 susceptibility. We evaluated the risk of allelic model (G vs. A), recessive model (GG vs. AA+AG), dominant model (GG+AG vs. AA), homozygous model (GG vs. AA), heterozygous model (AG vs AA), and over-dominant model (GG+AA vs AG). Stata 12.0 software was applied for data analysis. Heterogeneity was estimated with I^2 statistic and Cochran's Q test. I^2 was used to quantify the extent of heterogeneity (I^2<25% means low heterogeneity, 25≤I^2≤50% means moderate heterogeneity, and I^2>50% means high-level heterogeneity) (21, 22). A fixed-effects model (Mantel and Haenszel model) was applied to estimate *OR*s (95% *Ci*s) with low or moderate heterogeneity, otherwise, the random-effects model (Der Simonian and Laird) was used (23). The *Z* test was conducted to estimate the numerical significance of the combined *OR*. Hardy-Weinberg equilibrium analysis on genotype distribution of the control groups was carried out with a Chi-squared test. Sensitivity analysis was used to evaluate the stability of the results (24). The publication bias was evaluated by a funnel plot and Egger's test (25, 26). P<0.05 is considered significant.

RESULTS

Selected Articles and Characteristics

The pieces of literature selected are shown in Figure 1. 296 articles were identified by searching the databases above, and we excluded 245 articles by browsing the titles

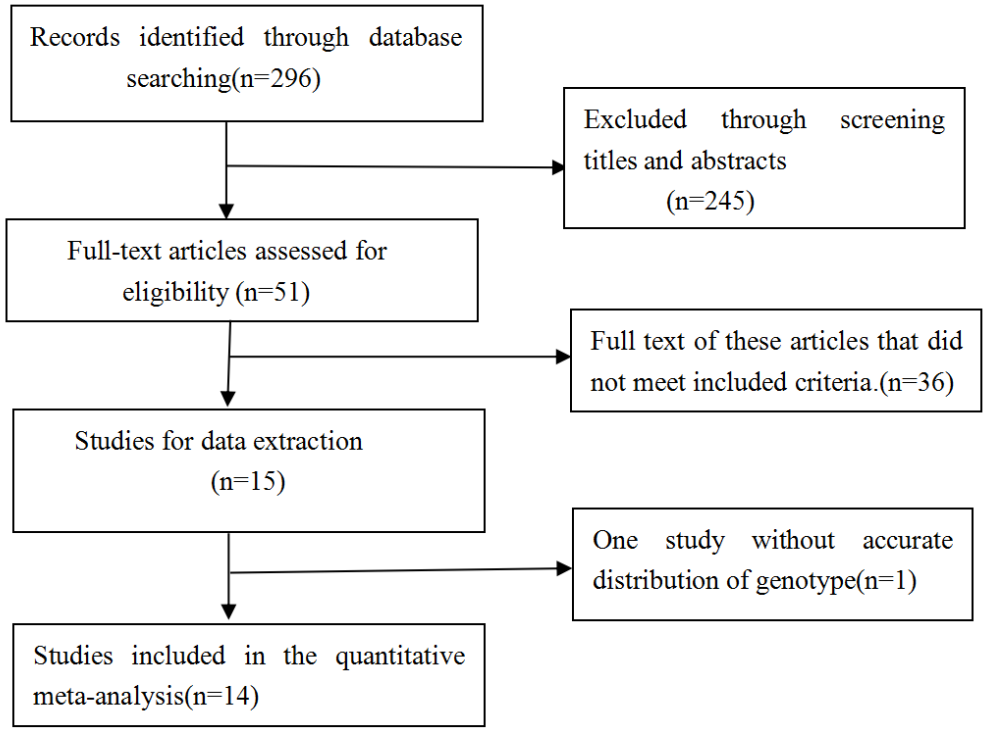

Figure 1. Flow chart of studies included in this meta-analysis

and abstracts. Of the remaining 51 articles, 15 articles were included in this analysis. One study did not provide accurate information on genotype distribution, thus, it was excluded (27). Finally, we included 14 studies in total, which involved 5 Caucasians, 4 Asians, 2 African-Americans, 1 Indian, 1 Ukrainian, and 1 unknown (or mixed) population. Among them, 9 studies provided 1082G/A genotypes, and 11 studies on 592C/A (alternative nomenclature: 597C/A) (28), and 6 studies included both. The details of eligible studies and the results of Hardy-Weinberg equilibrium analysis are summarized in Table 1.

All the studies met Hardy-Weinberg equilibrium except for one study (29). Although the deviation of the control groups from H-W equilibrium reflected the possibility of genotyping errors, population substructure, or selection bias (30), these results were not affected by excluding the study inconsistent with HWE (data were not shown). In summary, this study was adopted in the meta-analysis.

Quantitative Data Synthesis

IL-10-1082 G/A Polymorphism and HIV-1 Susceptibility

For -1082G/A polymorphism, nine studies including 1664 HIV patients and 2357 controls were involved. The significant heterogeneity was observed in heterozygous model (AG vs. AA: I^2=49.9%, P=0.035) and over-dominant model (GG+AA vs. AG: I^2=57.4%, P=0.012),

Table 1. Characteristics of the individual studies investigating the association of *1082G/A* and *592C/A* polymorphisms in IL-10 with HIV-1

Author	Year	Ethnicity	Country	No. of case /control	1-1 (case/ control)	1-2 (case/ control)	2-2 (case/ control)	HWE (*P*)
	1082G/A				GG	GA	AA	
Erikstrup C	2007	Shona.	Denmark	195/175	22/17	73/82	100/76	0.45
Shrestha S	2013	African-Americans	US	266/532	45/90	136/245	85/197	0.35
Ramezani A	2015	Caucasians	Iran	70/31	10/3	32/15	28/13	0.66
Freitas FB	2014	Caucasians, African	Brazil	216/294	14/24	79/111	123/159	0.46
Chatterjee A	2009	Asian	India	180/305	20/27	60/122	100/156	0.65
Affandi JS	2012	African-Americans	Australia	41/114	11/46	25/51	5/17	0.64
Affandi JS	2012	Caucasians	Australia	37/48	7/18	22/16	8/14	0.02
Kallas E	2015	Caucasians	Estonia	172/496	32/104	78/251	62/141	0.69
Ramaseri Sunder S	2012	Asian	India	227/102	11/2	120/43	96/57	0.06
Singh S	2016	Asian	India	260/260	21/21	119/125	120/114	0.1
	592C/A				CC	CA	AA	
Erikstrup C	2007	Shona.	Denmark	195/175	80/68	71/81	43/25	0.91
Shrestha S	2013	African-Americans	US	266/532	109/234	128/234	29/64	0.64
Ramezani A	2015	Caucasians	Iran	70/31	31/16	35/11	4/4	0.36
Sobti RC	2010	Asian	India	300/300	36/34	137/146	127/120	0.29
Chatterjee A	2009	Asian	India	180/305	67/140	74/122	39/43	0.05
Konenkov VI	2001	Caucasians	Novosibirsk	120/52	79/38	37/14	4/0	0.26
Kallas E	2015	Caucasians	Estonia	172/496	113/306	49/167	10/23	0.97
Corchado S	2013	Caucasians	Spain	88/51	43/24	38/21	7/6	0.67
Singh S	2016	Asian	India	260/260	106/109	115/122	39/29	0.55
Piddubna	2013	Ukraine	Ukraine	78/100	42/25	28/5	8/0	0.62
Harishankar M	2018	South Indian	India	100/122	27/50	51/54	22/18	0.59

HIV-1, human immunodeficiency virus-1; HWE, Hardy–Weinberg equilibrium

and random-effects model was conducted in the two models. Additionally, a fixed-effects framework was applied to the other models. The association was not significant between -1082G/A polymorphism and HIV-1susceptibility (allelic model (G vs. A): *OR (*95% *CI)*=0.968(0.878–1.067), P=0.510; recessive model (GG vs. AA+AG): *OR (*95% *CI)*=0.940(0.771–1.146), P=0.542; dominant model (GG+AG vs. AA): *OR (*95% *CI)*=0.967(0.846–1.106), P=0.624; homozygous model (GG vs. AA): *OR (*95% *CI)*=0.971(0.780–1.209), P=0.796; heterozygous model (AG vs AA): *OR (*95% *CI)*=0.988(0.797–1.224), P=0.910; over-dominant model (GG+AA vs AG): *OR (*95% *CI)*=0.969(0.781–1.201), P=0.773). The details are shown in Table 2 and Figure 2.

IL-10-592 C/A Polymorphism and HIV-1 Susceptibility

For -592C/A polymorphism, 11 studies

Table 2. Meta-analysis of the association between *1082G/A* and *592C/A* polymorphisms in IL-10 and the risk of HIV-1

Polymorphisms	Genetic model	Test of association			Test of heterogeneity		Egger's test		Effect model
		OR (95%CI)	Z	P	I^2 (%)	P_{het}	t	P	
-1082G/A	G vs. A	0.968(0.878,1.067)	0.66	0.51	17.6	0.281	-0.05	0.965	F
	GG vs. AA+AG	0.940(0.771,1.146)	0.61	0.542	0.3	0.435	-0.24	0.815	F
	GG+AG vs. AA	0.967(0.846,1.106)	0.49	0.624	40.3	0.089	0.80	0.447	F
	GG vs. AA	0.971(0.780,1.209)	0.26	0.796	0	0.712	0.79	0.454	F
	AG vs. AA	0.988(0.797,1.224)	0.11	0.91	49.9	0.035	1.09	0.309	R
	GG+AA vs. AG	0.969(0.781,1.201)	0.29	0.773	57.4	0.012	-1.40	0.198	R
-592C/A	C vs. A	0.876(0.796,0.965)	2.69	0.007	41.3	0.074	-1.51	0.164	F
	CC vs. AA+AC	0.882(0.770,1.010)	1.82	0.069	36.4	0.108	-1.75	0.113	F
	CC+AC vs. AA	0.793(0.664,0.948)	2.55	0.011	14.1	0.310	-0.45	0.666	F
	CC vs. AA	0.755(0.612,0.930)	2.63	0.008	15.3	0.298	-0.53	0.608	F
	AC vs. AA	0.820(0.679,0.991)	2.06	0.040	10.6	0.344	-0.05	0.961	F
	CC+AA vs. AC	1.009(0.887,1.148)	0.14	0.890	29.5	0.165	-1.91	0.088	F

HIV-1, human immunodeficiency virus-1; *OR*, odds ratio; *CI*, confidence interval; F, fixed-effect model; R, random-effect model.

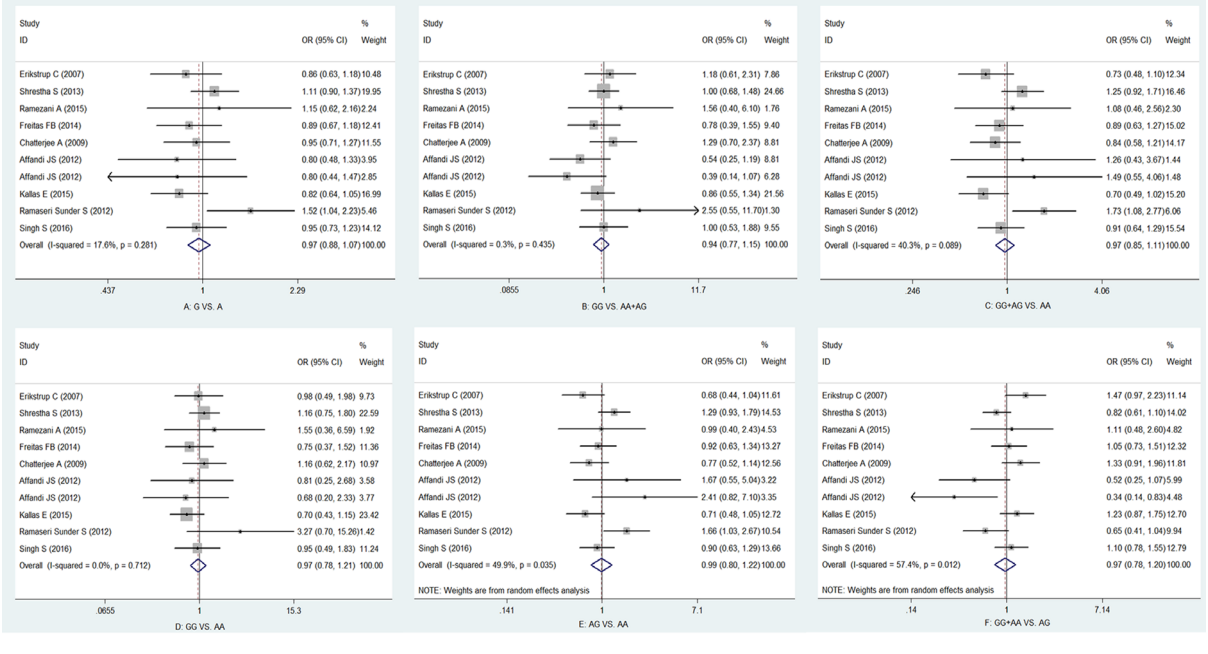

Figure 2. *ORs* and 95% *CIs* of individual studies and pooled data for the association between IL-10-1082G/A polymorphisms and HIV-1 susceptibility. (A: G VS. A; B: GG VS. AA+AG; C: GG+AG VS. AA; D: GG VS. AA; E: AG VS. AA; F: GG+AA VS. AG)

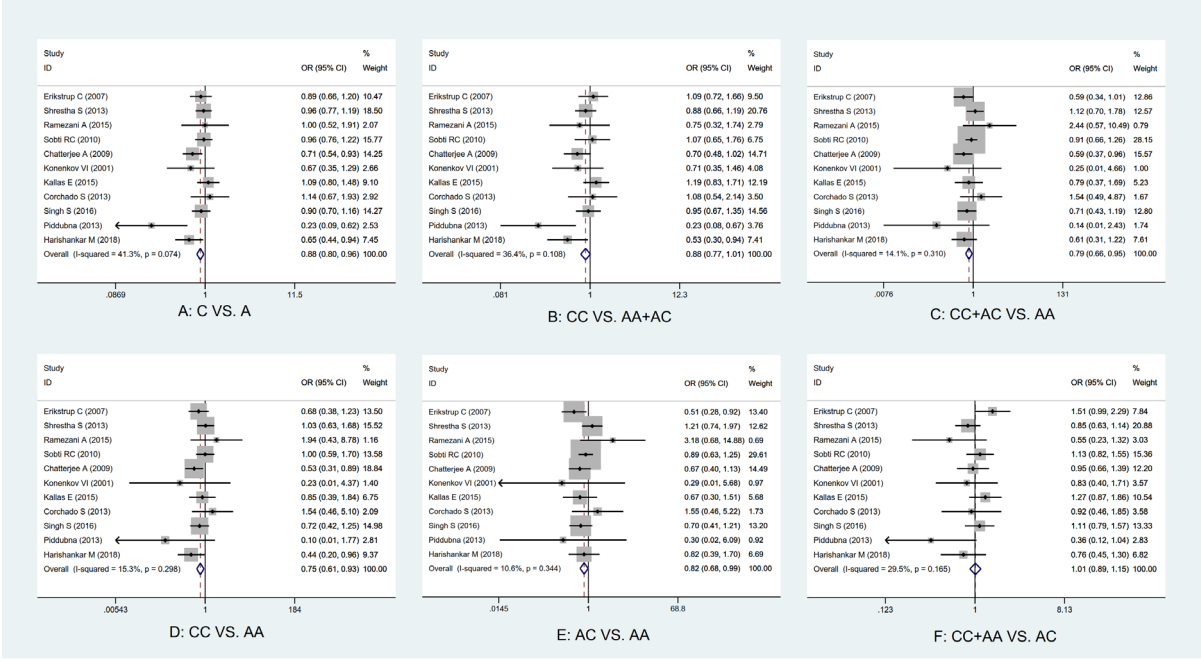

Figure 3. *ORs* and 95% *CIs* of individual studies and pooled data for the association between IL-10-592C/A polymorphisms and HIV-1 susceptibility. (A: C VS. A; B: CC VS. AA+AC; C: CC+AC VS. AA; D: CC VS. AA; E: AC VS. AA; F: CC+AA VS. AC)

including 1829 HIV patients and 2424 controls were involved. Fixed-effects model was conducted. Broadly, -592C/A polymorphism was related to HIV-1 infection in allelic model (C vs. A, *OR(*95% *CI)*=0.876(0.796–0.965), P=0.007), dominant model (CC+AC vs. AA: OR *(*95% *CI)*=0.793(0.664–0.948), P=0.011), homozygous model (CC vs. AA: OR *(*95% *CI)*=0.755 (0.612–0.930), P=0.008) and heterozygous model (AC vs. AA: OR *(*95% *CI)*=0.820 (0.679–0.991), P=0.040), except recessive model (CC vs. AA+AC: OR *(*95% *CI)*=0.882 (0.770–1.010), P=0.069) and over-dominant model (CC+AA vs. AC model: OR *(*95% *CI)*=1.009 (0.897–1.148), P=0.890). Table 2 and Figure 3 show these results.

Heterogeneity and Subgroup Analysis

The result of Cochran's Q statistic for heterozygous model (AG vs. AA) of IL-10-1082G/A showed that the p-value was 0.035 less than 0.1, and I^2 was 49.9%. For over-dominant model (GG+AA vs. AG) of IL-10-1082G/A, p was 0.012 less than 0.1 and I^2 was 57.4% (I^2>50%). Therefore, there existed heterogeneity in these two models. No heterogeneity was observed in the other p-values of Cochran's Q statistic and I^2 statistics. Subgroups analysis suggested that ethnicity might not be one of the reasons for heterogeneity. The details are shown in Figure S1 and Figure S2 in the supplement.

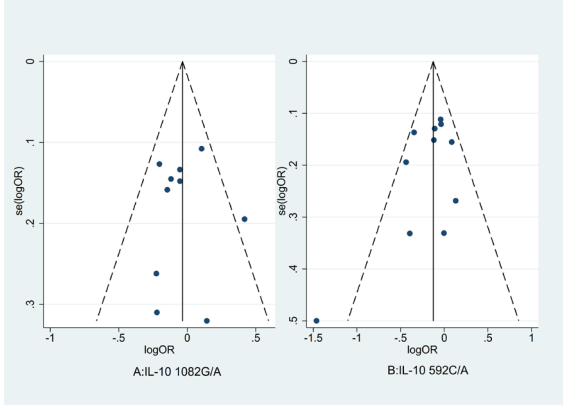

Figure 4. Publication bias in studies of the association between IL-10 polymorphisms and the risk of HIV-1 infection by funnel plot for allele model. (A. 1082G/A; B. 592C/A)

Publication Bias

Funnel plot and Egger's test were used to evaluate publication bias. No publication bias appeared. The funnel plots of allelic model in IL-10-1082G/A and -592C/A are presented in Figure 4. In addition, there were no circumstances that *P* was less than 0.05, an indication that that the publication bias was not significant (shown in Table 2).

Sensitivity Analysis

As shown in Figure 5, the results of

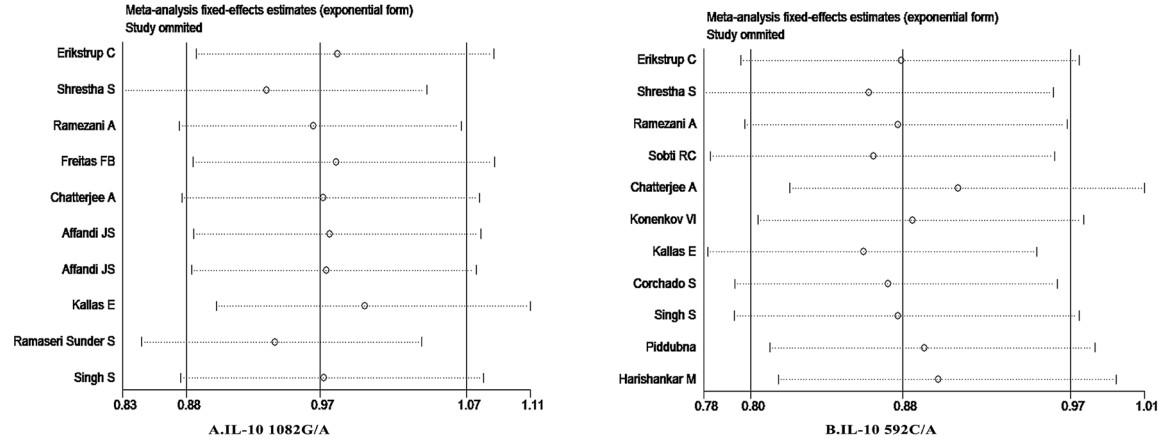

Figure 5. Sensibility analysis in studies of the association between IL-10 polymorphisms and the risk of HIV-1 infection for allele model. (A. 1082G/A; B. 592C/A)

allelic model in IL-10-1082G/A were kept statistically stable. The article that has the greatest influence on the overall pooled estimates of allelic model in IL-10-592C/A is the one conducted by Chatterjee A et al. (12). However, the moderate to high stability was drawn from sensitivity analysis, because the *OR*s (95% *CI*, P-value) were not much different before and after removing this article (0.88 (0.80–0.97, P=0.007) vs. 0.90 (0.82-1.00, P=0.056)).

DISCUSSION

Although the etiology of HIV infection is not clear up to this point, it is well known that genetic factors might be involved in the onset and disease progression. Numerous research have already been launched to look at genes in susceptibility to HIV-1, progression, outcome, such as chemokine receptor (CCR) 5-32, CCR2-64I, CCR5-P1, stromal cell-derived factor (SDF) 1-3A, mannose-binding lectin (MBL), HLA-A, -B, and -C (31). Additional HIV-related genes are presently being studied.

To date, there have been several reports on studying the link between IL-10 promoter polymorphisms and the risk of HIV-1, but conclusions were contradictory (12, 14-16, 32). Eriksturp C's study (14) indicated the protective role of IL-10−1082G while Sobti RC (16) and Ramezani et al. (32) found different results : the promoter polymorphisms in IL-10 gene were not related to HIV infection and AIDS progression. Chatterjee A's study (12) firstly reported IL-10−592C/A as risk factors and draw the same conclusion with Singh S (17) that IL-10 5'A might increase HIV-1 susceptibility and rapid progress to AIDS. Kallas E (15) suggested the protective roles of -1082A and -592A in resistance to HIV infection. The inconsistent results might be due to inadequate sample size, and different genetic backgrounds of subjects. Furthermore, it was reported that there existed a strong linkage disequilibrium between -819C/T and -592C/A polymorphisms (33, 34), so we just investigated the associations of -1082G/A and -592C/A polymorphisms with HIV susceptibility.

Therefore, we performed this program including 1664 patients and 2357 controls about-1082G/A and 1829 cases and 2424 controls about -592 C/A. Finally, no significant correlations were found between -1082G/A and HIV-1 susceptibility. Moreover, significant differences were found in allelic model (G vs. A), heterozygous model (AG vs. AA), homozygous model (GG vs. AA), and dominant model (GG+AG vs. AA), indicating that -592C/A polymorphism might be related to HIV-1 susceptibility.

Susceptibility to HIV was tightly correlated with the extent of exposure to the virus (35). IL-10 gene was considered to be related to the complex pathway of

HIV-1 entry and replication (36). IL-10, as a cytokine with anti-inflammatory and immunomodulatory, was involved in the stimulation and suppression of balanced immune responses. Furthermore, previous studies indicated that carriers with alleles of -592C or -1082G were related to increased IL-10 secretion, while -592A and -1082A alleles involved a low serum level of IL-10 (37-39). Studies in various populations all suggested the protective role of high-level IL-10 for HIV infection (12, 14, 40), and high-levels IL-10 would attenuate the decrease on $CD4^+$ T cells counts, which were the main target of HIV (41). Our findings were consistent with the observations above, further suggesting a link between IL-10 promoter polymorphisms and HIV-1.

Our study has had several unavoidable limitations, which must be pointed out. Firstly, we just reviewed English reports in PubMed, so, relevant articles in other languages or published in other databases might be missed. Secondly, the susceptibilities between polymorphisms and HIV-1 susceptibility were analyzed independently, but no gene-environment and gene-gene interactions were conformed. Thirdly, there existed various confounding factors correlated with HIV susceptibility, such as age, sex, etc., and they were not taken into consideration. Fourthly, we found that the sensitivity analysis results of allelic model in -592C/A gene site were not very stable based on Chatterjee A's study. However, subsequent investigation revealed that there were no variations in demographic, sample size, or procedures between this and the other studies included. Moreover, this study was evaluated with Newcastle-Ottawa Scale and the quality was high. Thus, we could not remove the study because it met the eligible criteria. Finally, the conclusion might be influenced by the fact that some controls had a history of HIV-1 exposure while some others did not. Aside from these limitations, there were several positive aspects to this meta-analysis. The most updated pieces of literature were strictly selected. Analytical results indicate stability with no publication bias.

CONCLUSION

-592C/A polymorphism might be associated with HIV-1 infection, while -1082G/A polymorphism is not. Additional research should be conducted to investigate the relationship between the combined impacts of numerous genes, and HIV-1 susceptibility in various ethnic populations.

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Conflict of Interest: None declared.

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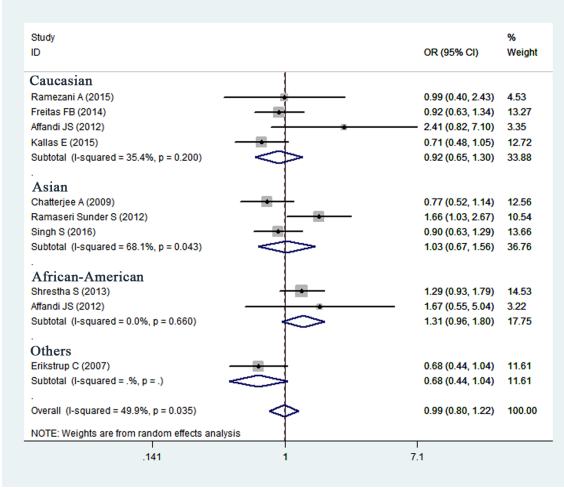

Figure S1. *OR*s and 95% *CI*s of individual studies and pooled data for heterozygous model (AG VS. AA) according to sources of ethnicity.

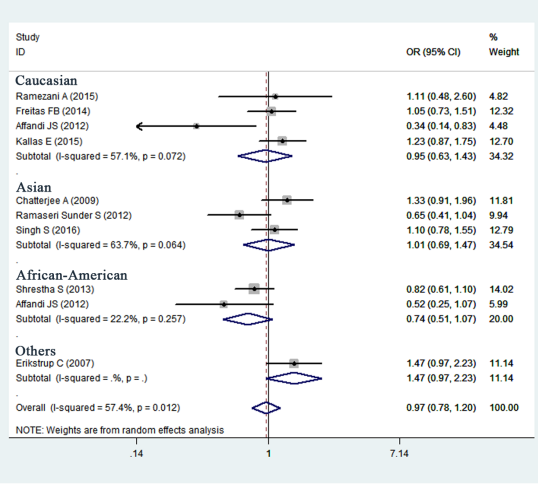

Figure S2. *OR*s and 95% *CI*s of individual studies and pooled data for over-dominant model (CC+AA vs. AC) according to sources of ethnicity.