Systematic Review and Meta-Analysis

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Association of toll-like receptor polymorphisms with acquisition of HIV infection and clinical findings

A protocol for systematic review and meta-analysis

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Abstract

Background: To find the relationship between toll-like receptor (TLR) gene variants and human immunodeficiency virus (HIV) infection and clinical findings, which could inform clinical decisions and vaccination strategies.

Method: Four databases were searched for articles that were published on or before Jul.1, 2020. Review Manager 5.3 software was applied to perform meta-analysis to explore.

Results: A total of 10 studies involving 20 genes, 3697 cases, and 6498 controls were included in this systematic review. TLR2 –196 to –174 Ins/Del (odds ratio [OR] = 1.562; $P = .002$), TLR4 rs4986790 (OR = 2.05; $P = .002$), TLR3 rs3775291 (OR = 0.25; $P = .03$), TLR7 rs179008 ($P = .002$), TLR7 rs2074109 (OR = 0.27, $P = .019$) were found associated with HIV infection. TLR2 –196 to –174, TLR4 rs4986790, TLR7 rs179008, TLR8 rs3764880, TLR9 rs352140 were found associated with clinical findings of HIV infection. We identified 5 case-control studies in meta-analysis, involving 695 cases and 729 controls on TLR7 rs179008 polymorphism, totaling 652 cases and 614 controls on TLR9 rs352140 polymorphism. In meta-analysis, we employed various genetic models. The T allele of TLR7 rs179008 was conferred the risk of HIV infection (T vs A: OR = 1.25, $P_A = .02$). An increased risk of HIV infection was found for individuals with the TLR9 rs352140 GG genotype (GG vs AA: OR = 1.50, $P_A = .04$).

Conclusions: The systematic review indicated that TLR7 rs179008 T allele provides risk effects for HIV infection. TLR9 rs352140 GG genotype may associate with HIV infection.

Abbreviations: 95% CIs = 95% confidence intervals, AIDS = acquired immunodeficiency syndrome, FPRP = false-positive report probability, GWAS = genome-wide association studies, HIV = human immunodeficiency virus, HWE = Hardy-Weinberg equilibrium, IRF-3 = interferon regulatory factor-3, NOS = Newcastle–Ottawa quality assessment scale, OR = odds ratio, SNPs = single-nucleotide polymorphism, TLR = toll-like receptor, TSA = trial sequential analysis.

Keywords: human immunodeficiency virus, infection, single nucleotide polymorphisms, systematic review, toll-like receptor

1. Introduction

Acquired immunodeficiency syndrome (AIDS) is a contagious and potentially fatal disease caused by the human immunodeficiency virus (HIV). It is now recognized that chronic, generalized immune activation is a major driving force for CD4+ T cell depletion and AIDS progression.[1] With similar risk exposure levels, the course of HIV-1 infection varies widely among individuals.[2–4] In addition, different AIDS patients whose rate of progression to immunodeficiency and associated complications exhibited a high differences. Without antiretroviral treatment, most HIV-positive patients develop AIDS within 10 years, but some infected persons progress to AIDS within 1 to 5 years and

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others may remain asymptomatic for over 20 years.[5–8] There is extensive heterogeneity among individuals in susceptibility to infection and the time to develop AIDS-defining diseases. Therefore, the genetic background of an individual might play an important role in acquisition of HIV and disease progression after HIV infection.[9] Using a combination of analyses is including genome-wide association studies (GWAS) have identified a number of common host genetic polymorphisms involved in HIV immunopathogenesis,[10–13] such as toll-like receptors (TLRs), interferon regulatory factor-3 (IRF-3) and tripartite motif 5a (TRIM5a) gene family.[14]

TLRs belong to the family of pattern recognition receptors and are important pathogen recognition receptors (PRRs).[15] They can recognize pathogen-associated molecular patterns and initiate signaling pathways that lead to the activation of the innate immune response, cytokines, and formation of the adaptive immune response.[16] To date, about 13 TLRs recognizing different pathogen-associated molecular patterns have been discovered,[17] 11 including in human.[18] Different TLRs have different structurally characterized, TLR1, 2,4, 5, 6, 10, and 11 are expressed on the cell surface while TLR3, 7, 8, and 9 reside in the endosomal compartments.[19] The TLRs on the cell surface sense conserved molecular motifs from a variety of organisms, primarily recognize bacteria, fungi parasites, and viruses.[15,20,21] Similarly, through the intracellular domains, TLRs function primarily to detect nucleic acids.[22] As innate immune sensors, TLRs are integral to resisting chronic and opportunistic infections. Mounting evidence implicates shows that single-nucleotide polymorphisms (SNPs) in TLRs link to various infectious diseases, such as tuberculosis (TLR2),[23] cytomegalovirus infection (TLR3, TLR9),[24] meningococcaemia (TLR4),[25] also including HIV infection.

Immune activation is a major determinant for AIDS, the stimulation of TLRs implicate a wide array of innate immune responses and inflammation and play an important role in controlling the pathogenesis of infections and their control.[26,27] They can trigger a complex cascade of signaling pathways in several cell types including dendritic cells, monocytes, macrophages neutrophils, and CD4 T lymphocytes, which are the target cells of HIV. There are now many evidences demonstrated the role of TLRs in HIV infection. Some studies provided TLR1,[28] TLR2,[29–32] TLR3,[31,33,34] TLR4,[29–33,35] TLR6,[31] TLR7/8,[31,33,36–38] and TLR9[33] have a functional role in HIV infection and disease. In addition, SNPs in TLR2,[39–43] TLR3,[39–42] TLR4,[39–43] TLR7,[39–41,44] TLR8,[39–41,45] and TLR9[39–43,46] have been evaluated for their effects on HIV acquisition and disease progression in various populations under a variety of study designs. However, some research samples are too small, the research focus is not the same, and even some research results are contradictory. Up to now, there is no systematic review on this aspect. Thus, to better assess the potential associations between TLR gene polymorphisms and HIV infection and clinical findings, we performed a systematic review of all relevant studies.

2. Materials and methods

2.1. Identification of eligible studies

We utilized Medline/PubMed, EMBASE, Web of Science, and the Cochrane Library until Jul.1, 2020. The following keywords were included in the search: "HIV" or "human immunodeficiency virus" or "AIDS" or "Acquired immunodeficiency syndrome" in combination with "polymorphism" or "SNP" or "variant" or "genotype" and in combination with "toll" or "TLR" or "toll-like receptor" or "toll-like receptor." The reference lists of retrieved studies and recent reviews were also manually searched for further relevant studies.

2.2. Inclusion and exclusion criteria

Studies in this meta-analysis must meet the following inclusion criteria:

(1) evaluation of the relationship between TLR polymorphisms and HIV infection;
(2) case-control study;
(3) studies with detailed genotype data in both cases and controls.

Exclusion criteria:

(1) duplication of previous publications;
(2) case reports, basic research, review, and other non-case-control studies;
(3) studies without detailed genotype data;
(4) did not deal with humans;
(5) subject is not an adult;
(6) non-English publications.

2.3. Data extraction

The data of all eligible studies were extracted by 2 investigators independently. The following data were recorded:

(1) name of first author;
(2) year of publication;
(3) ethnicity;
(4) genotyping methods;
(5) whether the genotypes of all component studies were tested for Hardy-Weinberg equilibrium (HWE);
(6) number of cases and controls;
(7) clinical findings.

Two authors checked the extracted data and reached to consensus on all the data. If a dissent existed, the third investigators would be involved to adjudicate the disagreements.

2.4. Quality assessment

We used a risk-of-bias tool modified from the Newcastle–Ottawa quality assessment scale (NOS) to assess the quality of individual reports.[47] The NOS is a scoring tool comprising patient selection, comparability of study groups, and ascertainment of outcome (See Table S, http://links.lww.com/MD/F402, supplementary content, which illustrates the evaluation criteria of quality scores). Quality scores ranged from 0 to 9 and the studies with more than 6 scores were considered better quality.

2.5. Trial sequential analysis (TSA) and false-positive report probability (FPRP) analysis

The reliability and authenticity of the results of meta-analysis were verified by TSA and FPRP. TSA parameter setting: type I error probability of 5%, type II error probability of 35%, and risk ratio reduction of 15% to calculate the Require Information Size (RIS).[48] FPRP parameter setting: threshold to 0.2, prior

probability assigned 0.1 and detect an odds ratio (OR) of 0.67/1.50 (protective/risk effects) for an association with genotypes under investigation. The significant result with an FPRP value less than 0.2 was considered a noteworthy finding. All the calculations to derive FPRP were performed with the Excel spreadsheet released by Wacholder et al.[49]

2.6. Statistical analysis

HWE was calculated for the control group of studies that did not describe HWE using the Chi-square test. The crude ORs and 95% confidence intervals (95% CIs) were calculated to investigate the association strength between polymorphisms and HIV infection for each study. Pooled OR were obtained from combination of single studies by allelic comparison, dominant model, recessive model, homozygote model, and heterozygote model. Heterogeneity among different studies was assessed by the Q test and I^2 test.[50] The heterogeneity was considered significant when P-value was less than .1. If P-value more than .10, fixed-effects models are adopted, otherwise random-effects models were used. Publication bias was tested by symmetrical funnel Begg plot analysis. All statistical analyses were performed with Review Manager 5.3 software, $P < .05$ was considered statistically significant.

3. Results

3.1. Characteristics of included studies

A total of 339 studies were acquired from above databases. After screening, 10 studies were met the inclusion criteria, which included 20 genes, totaling 3697 cases and 6498 controls (Fig. 1). These included 2, 1, 3, 4, 1, and 4 studies on TLR2, TLR3, TLR4, TLR7, TLR8, and TLR9, respectively. Meta-analysis was

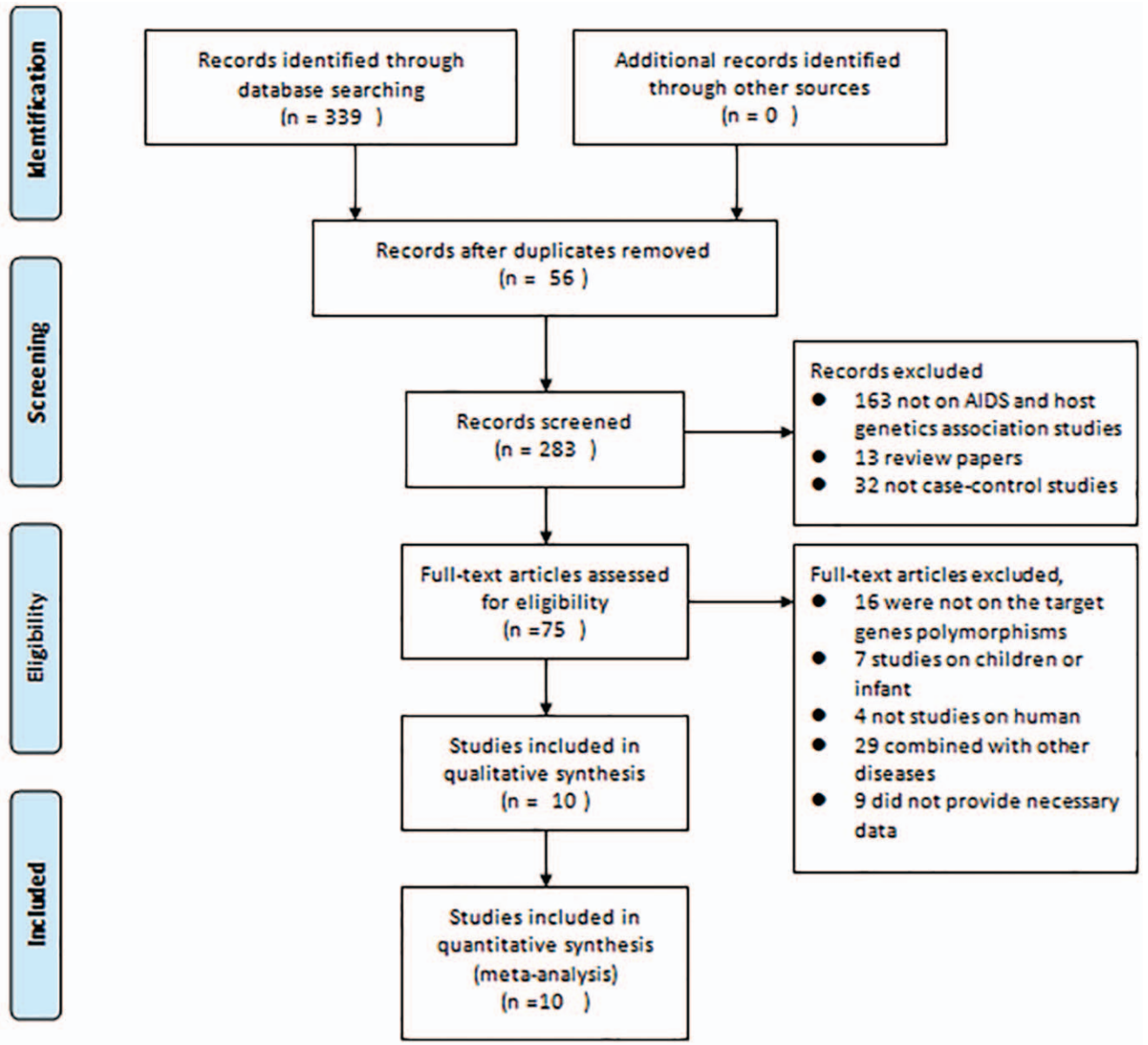

Figure 1. Chart of the literature search and selection process.

performed if one gene had at least three comparisons were available. These study participants were from diverse descents including Asian, European, and American. In all studies included, only the genotype distribution in the control of Joshi et al study was observed to deviate from HWE. Detailed characteristics of all the studies included were shown in Table 1. All included studies had relatively high NOS scores (ranging from 7–9) (Table 2).

3.2. Systematic review of TLR gene polymorphisms and acquisition of HIV infection

The study performed on an Indian cohort indicated that TLR2 –196 to –174 Ins/Del polymorphism is a risk factor for HIV-1 infection.[51] Compared with healthy controls, TLR2 Del mutant genotype (OR = 2.138; $P = .001$) and allele (OR = 1.562; $P = .002$) was higher in patients with HIV-1 infection. This correlation did not find in other TLR2 genes (rs5743708, rs5743704, rs12191786). Simultaneously, for the same research object observed that TLR4 rs4986790 was associated with HIV infection, G allele were significantly more frequent in HIV infection patients (OR = 2.05; $P = .002$), but not observed in TLR4 rs4986791.[52] The Caucasian cohort of the Huik study found that TLR3 rs3775291 display protective effect against HIV infection with T allele comparison (OR = 0.25; $P = .03$).[53] Oh et al showed that TLR7 rs179008 is associated with HIV infection, the mutant allele carriage frequency was significantly higher than that observed in healthy controls ($P = .002$),[44] but Shaikh et al did not find this association in Indian cohort.[54] However, Shaikh et al reported TLR 7 rs2074109 may be associated with HIV infection, and TLR7 rs2074109 G allele was significantly higher in healthy controls (OR = 0.27, $P = .019$).[54]

3.3. Systematic review of TLR gene polymorphisms and clinical findings

Among the genes of TLR2 (–196 to –174 Ins/Del, rs5743708, rs5743704, rs12191786), Vidyant found TLR2 Del homozygous genotype was lower in stage III (19.35%) as compared to stage I (50.87%; OR = 1.901) and stage II (43.05%; OR = 1.514) in patients with HIV. TLR2 Del homozygous genotype may be associated with reduced risk of HIV-1 disease progression.[51] The results of TLR2 (rs5743708, rs5743704) were same as Soriano-Sarabia et al results.[43] The remaining results of the Vidyant study pointed out TLR4 rs4986790 is associated with stage progression, but not observed in TLR4 rs4986791.[52] In an Omani cohort,[55] the relationship between TLR4 (1063A/G, 1363C/T) gene polymorphism and the CD4 and CD8 cell counts and viral load was not found. In the studies of TLR7 gene polymorphisms, Oh et al[44] showed TLR 7 rs179008 is associated high viral loads and lower baseline CD4 T-cell counts, which was consistent with Anokhin et al,[56] but inconsistent with Said et al.[57] TLR8 rs3764880 was conferred a significantly protective effect regarding progression of the disease.[45] The results reporting of the influence of the TLR9 rs352140 on disease progression are contradictory. A study performed in Spain[43] and American[58] HIV-infected cohort showed that TLR9 rs352140 is associated with lower CD4 count and higher viral load as rapid progression. In contrast, study in Omani showed that TLR9 rs352140 is associated with high CD4T cell count.[57] A recent study by Shaikh et al[54] showed that TLR9 rs352140 is associated with slow disease progression, but the relationship are not found in TLR7 (rs2074109, rs179009, chrX:12885280) and TLR9 (rs17846009, rs35342983, rs187084).

3.4. Meta-analysis results (Table 3)

3.4.1. TLR7 rs179008 polymorphism and acquisition of HIV infection. Three studies were included in the meta-analysis of this SNP, involving 695 cases and 729 controls. No heterogeneity was identified by Q-test and I-square statistic, so fixed-effects model was used. The T allele was shown the risk factor for HIV infection in the allelic model (T vs A: OR = 1.25, 95% CI: 1.04–1.50, $P_A = .02$). The forest plots were shown in Figure 2A. In addition, the TT and TA genotypes also had risk effect against HIV infection in the dominant models, heterozygote comparison (TT + TA vs AA: OR = 1.32, 95%CI: 1.03–1.70, $P_A = 0.03$, TA vs AA: OR = 2.21, 95%CI: 1.20–4.07, $P_A = .01$). The forest plots were shown in Figure 2B, E. No statistically significant results were found in recessive and homozygote models (TT vs TA + AA: OR = 1.17, 95%CI: 0.90–1.53, $P_A = 0.23$, TT vs AA: OR = 1.20, 95%CI: 0.92–1.57, $P_A = .17$). The forest plots were shown in Figure 2C, D. We performed the TSA, and RIS of 1951 was calculated. Z-curve crossed conventional boundary and TSA boundary, although the sample size did not reach RIS, which confirmed the certain results (Fig. 3).

3.4.2. TLR9 rs352140 polymorphism and acquisition of HIV infection. Four studies were included in the meta-analysis of this SNP, involving 652 cases and 614 controls. We found no heterogeneity existed, so still used fixed-effects model. The homozygote comparison showed GG genotype may be a risk factor for HIV infection (GG vs AA: OR = 1.50, 95%CI: 1.01–2.21, $P_A = .04$). The forest plots were shown in Figure 4D. We also performed comparison for the other 4 genetic models and no associations were found in any of these (G vs A: OR = 1.19, 95% CI: 0.99–1.43, $P_A = .07$, GG + GA vs AA: OR = 1.21, 95%CI: 0.89–1.64, $P_A = .22$, GG vs GA + AA: OR = 1.3, 95%CI: 0.95–1.77, $P_A = .11$, GA vs AA: OR = 1.19, 95%CI: 0.86–1.64, $P_A = .3$). The forest plots of the above-mentioned comparison were shown in Figure 4A, B, C, E, respectively. TSA was executed to count the RIS of 653. The result of TSA indicated that Z-curve crossed conventional boundary, but TSA boundary and RIS was not reached (Fig. 5). It means studies of high quality and large samples are needed to verify the relationship between TLR9 rs352140 polymorphism and HIV infection.

3.5. FPRP analysis

Table 4 shows the FPRP values for our positive results using different prior probability levels. When prior probability of 0.25 was adopted, significant association for TLR7 rs179008 (T vs A, TT + TA vs AA, TA vs AA) and TLR9 rs352140 (G vs A, GG vs. AA) was verified to be noteworthy.

3.6. Sensitivity analysis

To check the influence by the individual study on the overall ORs, we deleted each study once in every genetic model. The sensitivity analysis demonstrated that the TLR7 rs179008 and TLR9 rs352140 ORs were not statistically influenced, which validated the stability of our data.

Table 1

Characteristics of individual studies included in the review.

SNP	Author	Year	Country	Ethnicith	HWE	HIV-1 infect			Healthy controls			Susceptibility	Clinical findings
TLR2 2258 G/A Arg753Gln rs5743708						GG	GA	AA	GG	GA	AA		
	Soriano-Sarabia et al[48]	2008	Spain	Spanish	Y	364	4	0	152	3	0	NA	NS (VL, CD4)
	Vidyant et al[55]	2017	India	Indian		149	7	4	251	4	15	NS	NS
TLR2 1892 C/A Pro631His rs5743704						CC	CA	AA	CC	CA	AA		
	Soriano-Sarabia et al[48]	2008	Spain	Spanish	Y	349	19	0	186	8	0	NA	NS (VL, CD4)
	Vidyant et al[55]	2017	India	Indian		156	1	3	258	4	8	NS	NS
TLR2 2029 C/T Arg677Trp						CC	CT	TT	CC	CT	TT		
	Vidyant et al[55]	2017	India	Indian		136	24	0	214	57	0	NS	NS
TLR2 Ins/Del 196 to -174						Ins/Ins	Ins/Del	Del/Del	Ins/Ins	Ins/Del	Del/Del		
	Vidyant et al[55]	2017	India	Indian		85	9	66	140	79	51	Association with HIV-1 infection	Associated with reduced risk of disease progression.
TLR3 rs3775291						CC	CT	TT	CC	CT	TT		
	Huik et al[57]	2013	Caucasian	Caucasian		80	76	16	294	287	89	Protective effect against HIV infection	NA
TLR4 Asp299Gly 896A/G rs4986790						AA	AG	GG	AA	AG	GG		
	Soriano-Sarabia et al[48]	2008	Spain	Spanish	Y	322	43	3	171	26	2	NA	NS (VL, CD4)
	Vidyant et al[56]	2018	India	Indian		120	37	3	234	34	2	Associated with HIV infection	Association with stage progression
TLR4 Thr399Ile 1196C/T rs4986791						CC	CT	TT	CC	CT	TT		
	Soriano-Sarabia et al[48]	2008	Spain	Spanish	Y	320	44	4	173	24	2	NA	NS (VL, CD4)
	Vidyant et al.[56]	2018	India	Indian		141	18	1	246	23	1	NS	NS
TLR4 1063A/G						AA	AG	GG	AA	AG	GG		
	Said et al[59]	2016	Omani	Omani	Y	57	7	4	89	11	0	NA	NS (VL, CD4, CD8)
TLR4 1363C/T						CC	CT	TT	CC	CT	TT		
	Said et al[59]	2016	Omani	Omani	N	59	8	1	91	9	0	NA	NS (VL, CD4, CD8)
TLR 7 Gln11Leu (A/T) rs179008						AA	AT	TT	AA	AT	TT		
	Oh et al[49]	2009	German	Germany		549	24	161	433	9	103	Associated with HIV infection	Association with high viral loads and lower CD4 T-cell counts
	Said et al[61]	2014	Omani	Omani	Y	50	7	6	89	4	7	NA	association with high CD4T cell count
	Shaikh et al[58]	2019	India	Indian	Y	60	4	1	76	3	5	NS	NS
						Ala/Ala	Ala/Val	Val/Val	Ala/Ala	Ala/Val	Val/Val		
TLR7 Ala448Val rs5743781	Oh et al[49]	2009	German	Germany	Y	732	0	2	539	0	6	NS	NS
						TT	TG	GG	AA	AG	GG		
TLR 7 T-120G rs2302267	Oh et al[49]	2009	German	Germany	Y	687	0	47	515	0	30	NS	NS
						AA	AG	GG	AA	AG	GG		
TLR 7 A/G rs2074109	Shaikh et al[58]	2019	India	Indian	Y	61	4	0	73	4	7	May association with HIV infection	NS
						TT	TC	CC	TT	TC	CC	NS	NS
TLR7 T/C rs179009	Shaikh et al[58]	2019	India	Indian	N	65	0	0	82	0	2		
						TT	TC	CC	TT	TC	CC	NS	NS
TLR7 rs-Not allotted T/C chrX:12885280	Shaikh et al[58]	2019	India	Indian	Y	65	0	0	83	1	0	NS	NS
						AA	AG	GG	AA	AG	GG		
TLR8 A1G rs3764880	Oh et al[50]	2008	Germa	German		580	20	182	412	20	118	NS	Confers protective effect regarding progression of the disease
						GG	GA	AA	GG	GA	AA		
TLR9 1635G/A rs352140	Soriano-Sarabia et al[48]	2008	Spain	Spanish	Y	81	198	86	40	120	54	NA	Associated with lower CD4 count and higher viral load
	Said et al[61]	2014	Omani	Omani	Y	16	34	13	15	54	31	NA	Association with high CD4T cell count
	Joshi et al[62]	2019	America	American	NA	13	28	9	4	17	8	NA	Associated with lower CD4 counts in HIV positive patients
	Shaikh et al[58]	2019	India	Indian	Y	22	25	9	37	34	18	NA	Associated with slow disease progression
						GG	GT	TT	GG	GT	TT		
TLR 9 G/T rs17846009	Shaikh et al[58]	2019	India	Indian	Y	54	2	0	82	7	0	NS	NS
						GG	GA	AA	GG	GA	AA		
TLR9 G/A rs35342983	Shaikh et al[58]	2019	India	Indian	Y	54	2	0	86	3	0	NS	NS
						GG	GA	AA	GG	GA	AA		
TLR9 1486C/T rs187084	Joshi et al[62]	2019	America	American	NA	13	30	7	10	14	5	NS	May associate with disease progression

HIV = human immunodeficiency virus, HWE = Hardy–Weinberg equilibrium, NA = not available, NS = not significant, SNP = single nucleotide polymorphism.

Table 2

Newcastle-Ottawa Scale (NOS) quality assessment of included articles.

Author	Year	Selection score (4 Points)	Comparability score (2 Points)	Outcome score (3 Points)	Total score (9 Points)
Soriano-Sarabia et al[48]	2008	4	2	1	7
Oh et al[50]	2008	4	2	2	8
Oh et al[49]	2009	4	1	2	7
Huik et al[57]	2013	3	2	3	8
Said et al[61]	2014	4	2	1	7
Said et al[59]	2016	4	2	3	9
Vidyant et al[55]	2017	4	2	2	8
Vidyant et al[56]	2018	4	2	2	8
Joshi et al[62]	2019	4	1	2	7
Shaikh et al[58]	2019	4	2	1	7

Selection Score including; (1) Representativeness of the exposed cohort; (2) Selection of the nonexposed cohort; (3) Ascertainment of exposure; (4) Demonstration that outcome of interest was not present at start of study. Outcome Score including; (1) Assessment of outcome; (2) Was follow-up long enough for outcomes to occur; (3) Adequacy of follow up of cohorts.

3.7. Publication bias

Based on symmetrical funnel plots analysis of TLR9 rs352140, no evidence of publication bias was observed (Fig. 6). Owing to the limited number of included studies, funnel plots analysis of TLR7 rs179008 was not performed.

4. Discussion

It is well known that HIV can attack the human immune system and then cause chronic activation of the immune system in association with dysfunction of cellular and humoral immune responses and failure to effectively control virus replication.[59,60] Considerable variability exists among individuals in their susceptibility to HIV infection and subsequent clinical findings. Genetic variants of TLRs may influence susceptibility of HIV infection and disease outcome. To better understand the relationship between TLRs and HIV infection, we performed this systematic review.

In the present study, we totally pooled 10 articles, some of which have been proved TLR polymorphisms associated with HIV infection and clinical findings. For example, Vidyant et al has successive reported TLR2 –196 to –174 Ins/Del (Del mutant genotype, allele) and TLR4 rs4986790 (heterozygous genotype and the mutant allele G) were associated with HIV infection.[51,52] A study performed on an Indian cohort study showed that TLR7 rs2074109 may have role in association with HIV infection.[54] Meanwhile, in this Indian cohort study also reported TLR7 rs179008 were not associated with HIV infection, which is the opposite of the conclusion of the Germany cohort.[44] The reason for this contradictory result may be due to the different ethnicity. In our study, we found TLR7 rs179008 polymorphism may be associated with increased HIV infection, which is consistent with a previous study.[44] We found TLR7 rs179008 on T allele was the risk factor for HIV infection. Subsequently, significant association of TLR7 rs179008 polymorphism with HIV infection was identified in the dominant model and heterozygote model. Although the relationship between TLR9 rs352140 and HIV infection has not been studied in these articles, we found the TLR9 rs352140 GG genotype was a risk factor for HIV infection by meta-analysis. The authenticity of our meta-analysis results was verified by TSA and FPRP.

Much of the data comes from genetic analysis of populations that have an extreme phenotype in the clinical findings of HIV-1 infection, including viral load, CD4/CD8 cell counts, and disease progression. During the course of immune activation, activated T cells are produced as viral targets, further driving viral replication, and CD4 cell depletion. Immune activation and the above clinical findings are closely related in HIV-infected subjects. Genetic variants of the TLR gene are thought to regulate immune activation in HIV infection. Vidyant et al found that TLR2 Del homozygous genotypes were lower in low CD4 T-cell counts as compared to high CD4 T-cell counts and is associated with reduced risk of HIV-1 disease progression.[51] The TLR7 rs179008 and TLR9 rs352140 polymorphism are the most frequently studied in clinical findings of HIV infection. TLR7 rs179008, TLR9 rs352140 were linked to the high viral loads and

Table 3

Meta-analysis of the association between *TLR7, TLR9* polymorphisms, and HIV infection.

SNP	Included studies	Genetic model	OR	95%CI	I^2 (%)	P_H	Z	P_A
TLR7 Gln11Leu rs179008 (A>T)	3	Allelic (T vs. A)	1.25	1.04–1.50	41	0.18	2.42	0.02
	3	Dominant (TT+TA vs. AA)	1.32	1.03–1.70	0	0.40	2.20	0.03
	3	Recessive (TT vs. TA+AA)	1.17	0.90–1.53	5	0.35	1.19	0.23
	3	Homozygote (TT vs. AA)	1.20	0.92–1.57	8	0.34	1.37	0.17
	3	Heterozygote (TA vs. AA)	2.21	1.2.-4.07	0	0.81	2.56	0.01
TLR9 1635G/A rs352140 (G>A)	4	Allelic effect (G vs. A)	1.19	0.99–1.43	0	0.54	1.80	0.07
	4	Dominant (GG+GA vs. AA)	1.21	0.89–1.64	0	0.56	1.22	0.22
	4	Recessive (GG vs. GA+AA)	1.30	0.95–1.77	0	0.43	1.61	0.11
	4	Homozygote (GG vs. AA)	1.50	1.01–2.21	0	0.46	2.03	0.04
	4	Heterozygote (GA vs. AA)	1.19	0.86–1.64	0	0.78	1.04	0.30

CI = confidence interval, OR = odd ratio, P_A = adjusted *P* value ($P_A < .05$ means statistically significant), P_H = *P* value of heterogeneity, SNP = single nucleotide polymorphism.

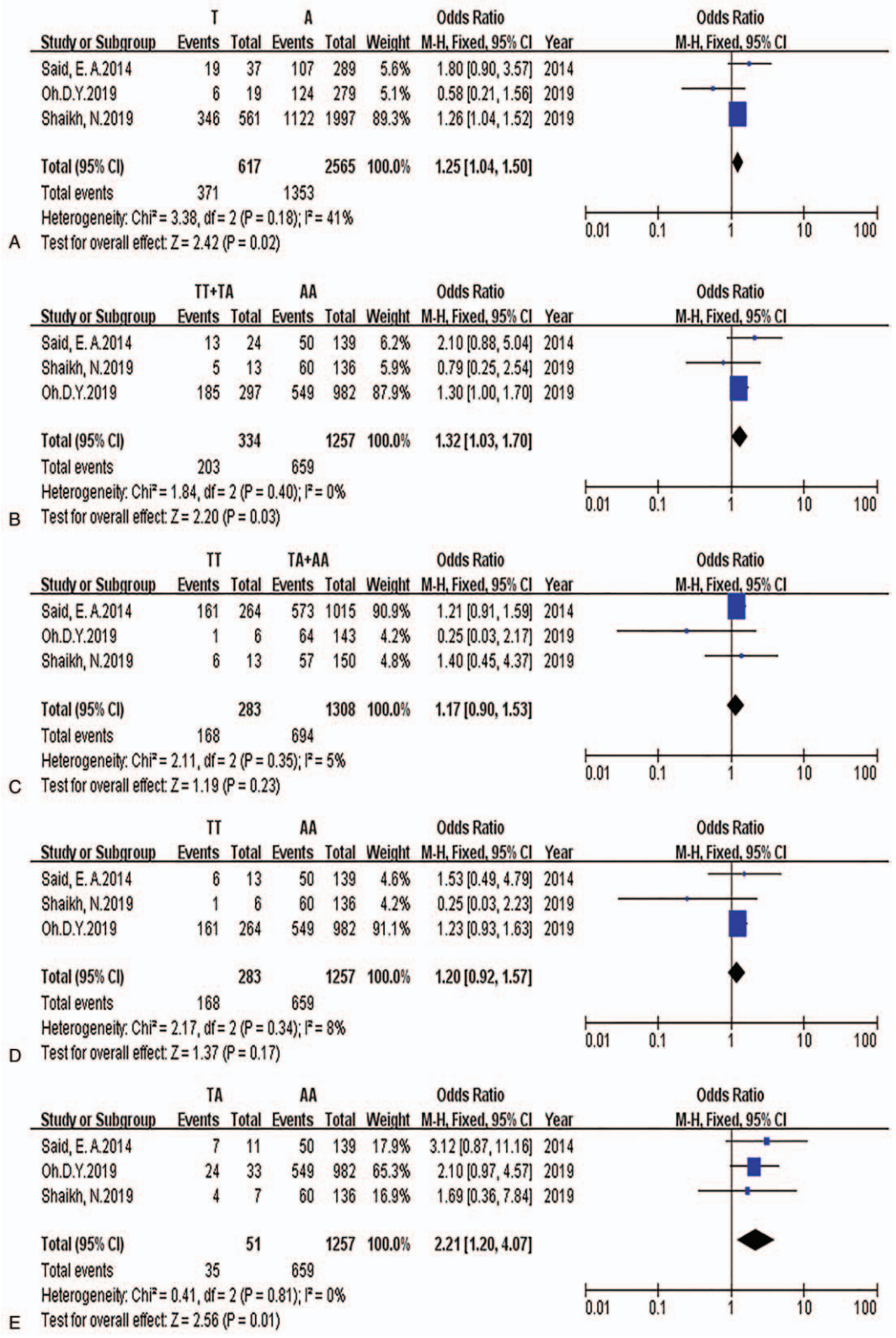

Figure 2. Forest plot of the association between TLR7 rs179008 and HIV infection for all five models. (A) Allelic model; (B) Homozygote comparison; (C) Heterozygote comparison; (D) Dominant model; (E) Recessive model.

lower CD4 T-cell counts in Germany, Spanish, American cohort respectively.[43,44,58] However, above results were in contrast to findings of Said et al.[57] These inconsistent findings may be due to ethnicity, sample size, or sampling error. Therefore, we need more research to expand the sample size for meta-analysis and ethnicity subgroup analysis to get more reliable conclusions.

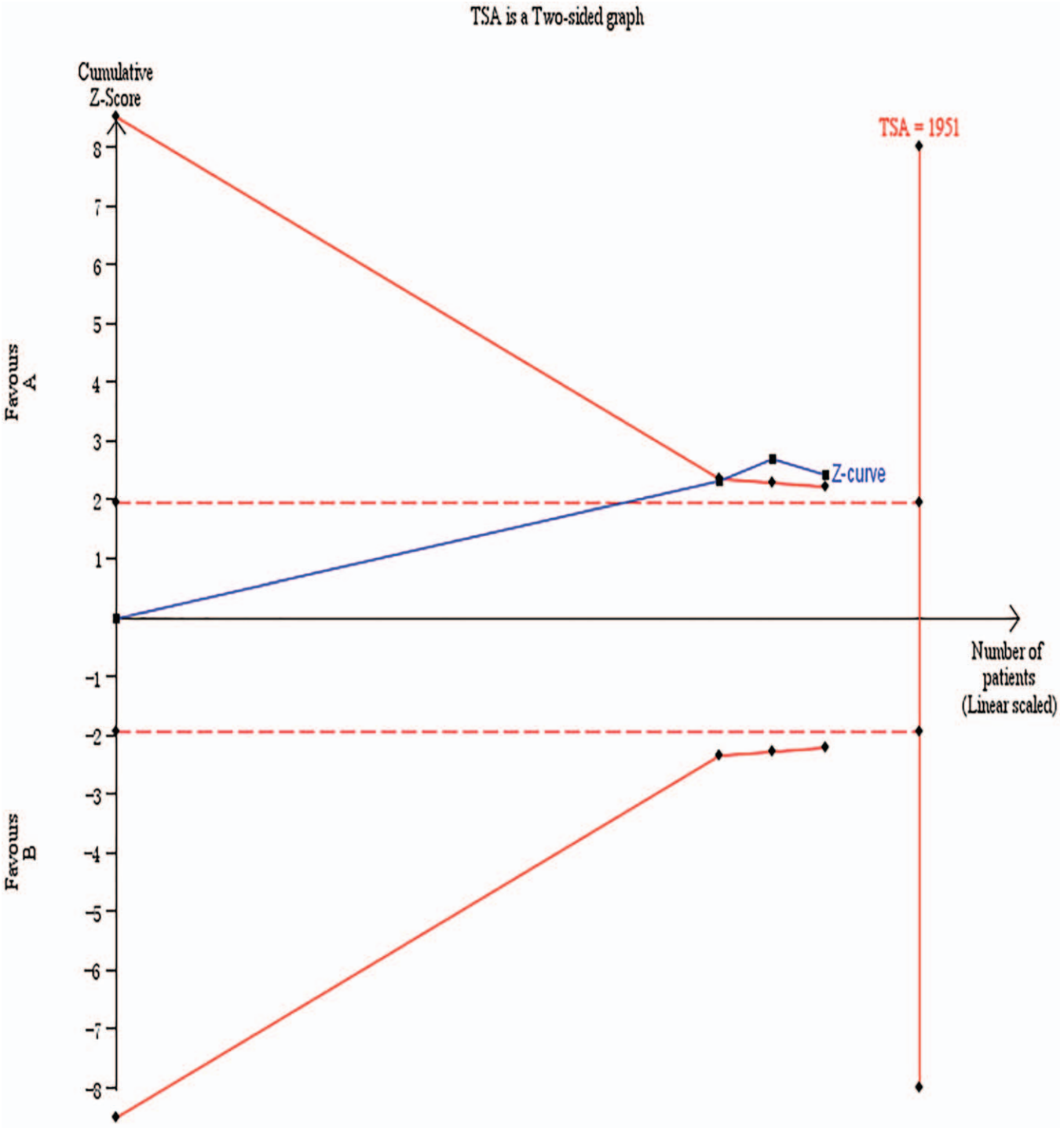

Figure 3. Trial sequential analysis for TLR7 rs179008 polymorphism under the allele contrast model.

HIV pathogenesis is a multifactorial and complex phenomenon and the large portion of variability in the natural history of HIV remains unexplained and influence disease outcome are still largely unknown. For example, we all know that AIDS patients with low immunity often tend to have tumors. HIV-AIDS is the most common cause of acquired immune deficiency syndrome and the most important risk factor for the malignant lymphoma. The majority of HIV-related lymphomas originate from germinal center B cells or postgerminal center B cells.[61] In the last years, experimental and clinical studies have shown that chronic inflammation, immune stimulation/deregulation, and oxidative stress are involved in the lymphomagenesis/lymphoproliferative disorders. The chronic inflammation transcription factor NF-kB activation - inflammatory cytokines release -ROS generation -oxidative stress - genomic instability -clonal volution link.[62] The results of Amelia Maria Gaman et al suggest that oxidative stress may be associated with the stage of advanced diffuse large B cell lymphoma.[63] Oxidative stress is involved in a variety of

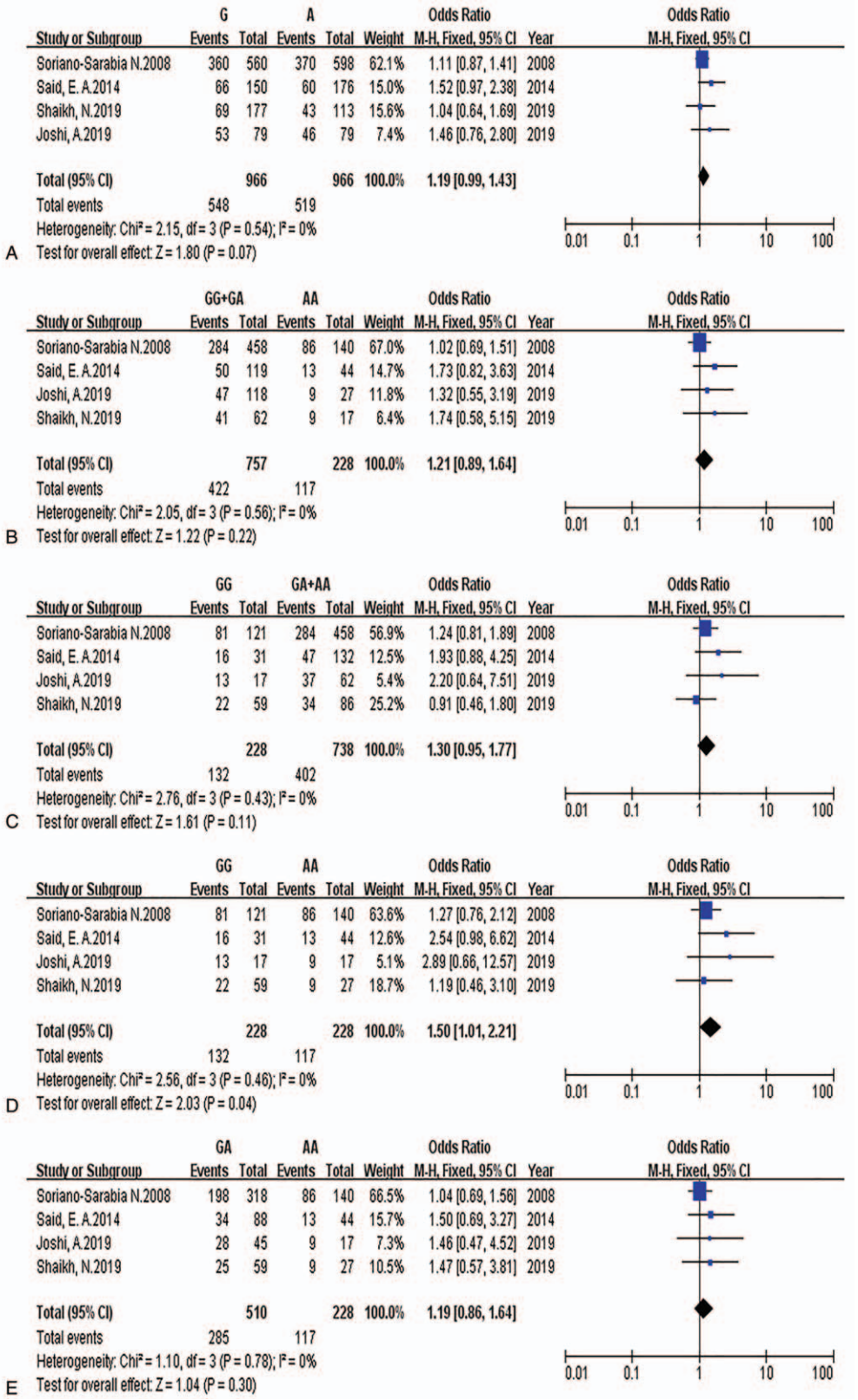

Figure 4. Forest plot of the association between TLR9 rs352140 and HIV infection for all five models. (A) Allelic model; (B) Homozygote comparison; (C) Heterozygote comparison; (D) Dominant model; (E) Recessive model.

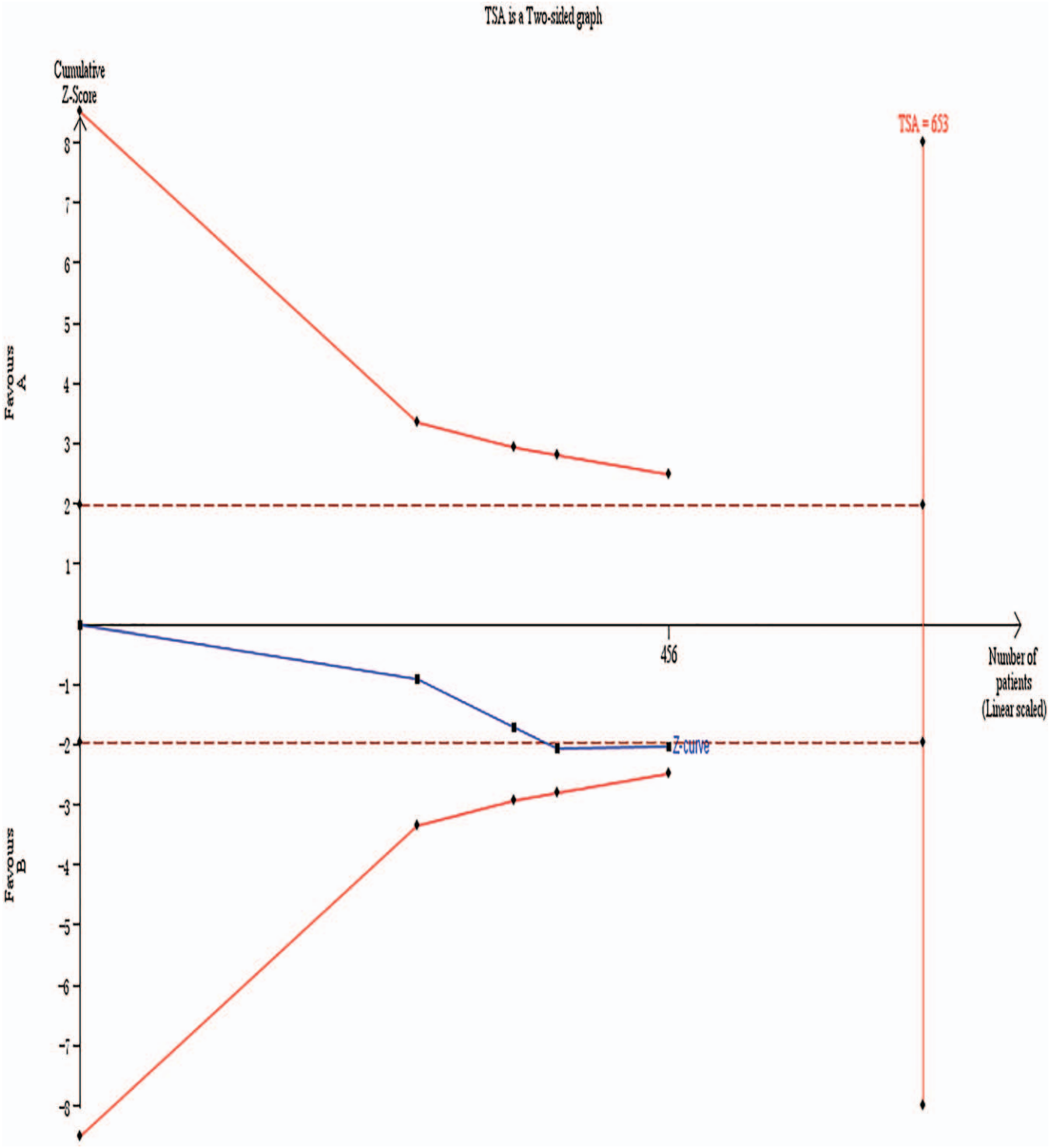

Figure 5. Trial sequential analysis for TLR9 rs352140 polymorphism under the homozygote comparison.

human diseases and disorders, including apoptosis and carcinogenesis. The antioxidant capacity of the human body decreases with age.[64] Therefore, the link between the HIV infection and lymphomagenesis/lymphoproliferative disorders can also be mediated by chronic inflammation and oxidative stress. It may also be related to the pathogenic properties of the virus itself, environmental factors, rare genetic variants, and other immune factors. The differences between studies may also reflect the variable nature of HIV infection among genetically different individuals. It is clear that the function and impact of genetic polymorphisms differ according to race and ethnicity. The risk of transmission and progression depends on multiple interactions between virus and host, and no single genetic variant is a crucial factor in HIV pathogenesis.

Table 4

False-positive report probability values for associations between *TLR7, TLR9* polymorphism and HIV infection.

SNP	Genetic model	OR	95%CI	*P*	Power	Prior probability				
						.25	.1	.01	.001	.0001
TLR7 Gln11Leu rs179008 (A>T)	Allelic (T vs A)	1.25	1.04–1.50	.016	1.000	.047	.129	.620	.943	.994
	Dominant (TT+TA vs AA)	1.32	1.03–1.70	.031	0.999	.086	.221	.757	.969	.997
	Recessive (TT vs TA+AA)	1.17	0.90–1.53	.251	1.000	0.430	.693	.961	.996	1.000
	Homozygote (TT vs AA)	1.20	0.92–1.57	.184	1.000	.355	.623	.948	.995	.999
	heterozygote (TA vs. AA)	2.21	1.2.-4.07	.011	0.374	.080	.208	.743	.967	.997
TLR9 1635G/A rs-352140 (G>A)	Allelic (G vs A)	1.19	0.99–1.43	.063	1.000	.160	.364	.863	.984	.998
	Dominant (GG+GA vs AA)	1.21	0.89–1.64	.219	0.999	.397	.664	.956	.995	1.000
	Recessive (GG vs GA+AA)	1.30	0.95–1.77	.096	0.997	.224	.463	.905	.990	.999
	Homozygote (GG vs AA)	1.50	1.01–2.21	.040	0.927	.115	.281	.811	.977	.998
	heterozygote (GA vs AA)	1.19	0.86–1.64	.288	0.999	.464	.722	.966	.997	1.000

CI = confidence interval, OR = odds ratio, *P* = Chi-square test was adopted to calculate the genotype frequency distributions; power, Statistical power was calculated using the number of observations in the subgroup and the OR and *P* values in this table.

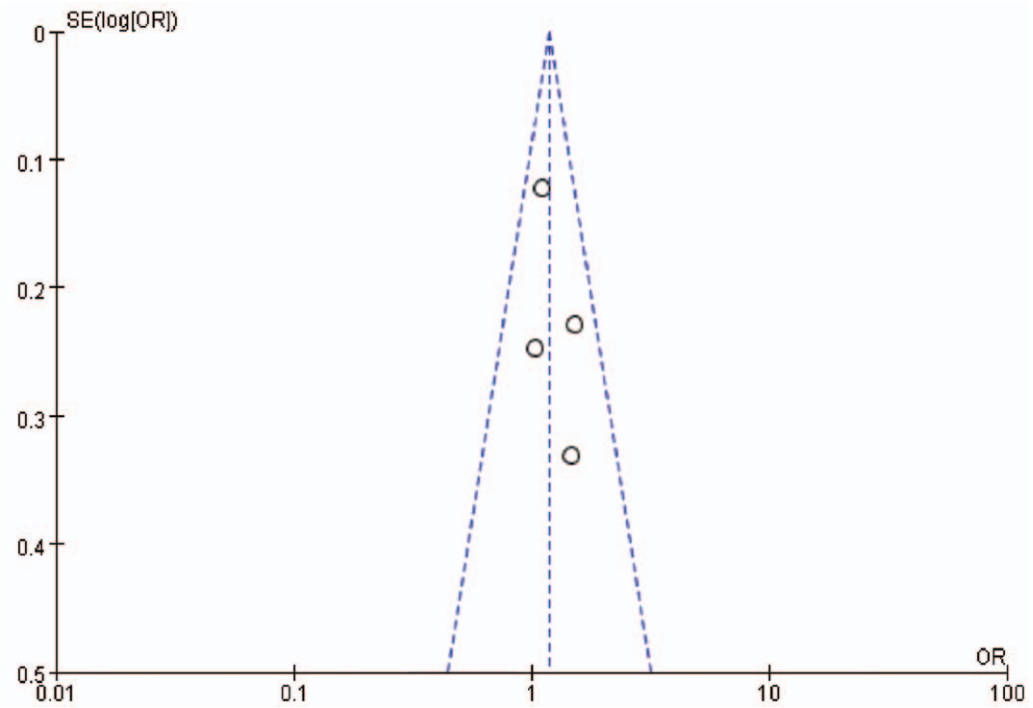

Figure 6. Begg funnel plot to detect publication bias analysis for TLR9 rs352140 polymorphism under the Allelic model.

As per our knowledge, this is the first and the most comprehensive systematic review about TLR polymorphisms association with HIV infection. Moreover, most of included studies had acceptable quality and had no significant heterogeneity. However, there were also some limitations in our study that should be considered when explaining the present results. First, because only a relatively small number of studies have investigated the roles of TLR polymorphisms in HIV infection, the number of studies included in the systematic review lacked of sufficient data to detect associations within ethnic groups. Future research with diverse demographic and clinical characteristics is necessary in ethnically diverse populations. Second, analysis was only based on genotyping data. It is impossible for only single genetic polymorphism to significantly contribute to the occurrence and development of this disease. Lastly, limiting the study to English language articles may have potentially led to a language bias.

5. Conclusions

In summary, this systematic review aimed to summarize the effects of the most commonly investigated TLR SNPs in relation to HIV infection. Our results suggested that TLR7 rs179008 T allele is the risk of HIV infection. TLR9 rs352140 GG genotype may associate with increasing HIV infection. Our study may have implications for the individual risk assessment of patients infected with HIV, meanwhile, this results is benefit to identify new targets for HIV preventative and therapeutic interventions.

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Writing – original draft: Han Shi.
Writing – review & editing: Hongyan He, Changfeng Sun, Juan Fu, Dipritu Ghosh, Cunliang Deng, Yunjian Sheng.

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