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Association Between miR-146a rs2910164 Polymorphism and Tuberculosis Susceptibility: A Comprehensive Meta-Analysis

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ABSTRACT

Prior research has indicated a potential link between the *miR-146a* rs2910164 genetic variant and an individual's susceptibility to pulmonary tuberculosis (TB). Nevertheless, the evidence from various studies is contradictory and has not yielded a consensus. This meta-analysis was therefore conducted to systematically assess the relationship between this specific single nucleotide polymorphism (SNP) and the risk of developing tuberculosis.

A systematic literature search was performed utilizing the electronic databases PubMed, Web of Science, Scopus, and ISI to capture all relevant publications available through April 2024. To ensure comprehensive coverage, the reference lists of retrieved full-text articles were also manually scrutinized. For the quantitative synthesis, pooled odds ratios (ORs) with their corresponding 95% confidence intervals (CIs) were computed to determine the overall effect estimates. The chi-square (χ^2) test and the I^2 statistic were applied to assess and quantify heterogeneity. This meta-analysis included 6363 individuals (2904 TB patients and 3459 healthy controls) from eight case–control studies. The pooled effect estimates across all genetic inheritance models (e.g., dominant model: OR = 0.971, 95% CI: 0.884–1.068) did not reveal a significant link between the rs2910164 polymorphism and susceptibility to tuberculosis. The analysis revealed considerable heterogeneity across most genetic models, as indicated by I^2 statistics exceeding 70%. Conversely, statistical tests found no evidence of publication bias. The collective evidence from this analysis does not support a significant association between the *miR-146a* rs2910164 G>C variant and tuberculosis susceptibility. Confirmation of this null association necessitates future validation in large-scale, rigorously designed studies.

***Keywords*:** Tuberculosis, *miR-146a*, rs2910164, microRNA polymorphism, genetic susceptibility, meta-analysis

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Introduction

Tuberculosis (TB) is a communicable disease transmitted primarily via airborne particles. Despite the availability of effective treatments, TB is responsible for nearly 1.5 million global fatalities annually. A substantial contributor to this mortality is multidrug-resistant tuberculosis (MDR-TB), which presents particular challenges in affected populations. (1-3). Following inhalation of *Mycobacterium tuberculosis* (MTB), an estimated 5–15% of infected individuals will progress to active tuberculosis over the course of their lifetime. (4).

Following infection, tuberculosis may persist in a latent state for extended periods; however, disease progression to active TB occurs predominantly within the initial 24-month period post-exposure. (5, 6). Pulmonary disease is the most common manifestation in patients infected with MTB, although it can also affect other organs (7). To date, numerous studies have demonstrated that genetic factors may significantly influence TB, and the importance of genetic predisposition is gaining more attention and recognition (8, 9). MicroRNAs (miRNAs) belong to a class of short, non-coding RNA molecules, typically approximately 22 nucleotides in length. They orchestrate key cellular functions through complementary base-pairing with the 3'-untranslated regions (3'-UTRs) of target messenger RNAs (mRNAs), a mechanism that directly modulates gene expression. This engagement enables them to affect the expression of particular genes. Additionally, miRNAs contribute to a diverse spectrum of physiological processes (10, 11). Beyond TB, *miR-146a* plays a pivotal role in a broad spectrum of diseases (12, 13).

miRNAs serve as pivotal regulators in adaptive immunity by directing T cell differentiation and functional dynamics. Concurrently, they exert substantial influence over innate immune mechanisms, modulating the antimicrobial activity of macrophages, dendritic cells, and natural killer (NK) cells all critical components of the host defense against mycobacterial invasion. MTB has evolved strategies to co-opt these host miRNAs, subverting antibacterial signaling cascades to enhance its virulence and persistence.

Among these immunoregulatory miRNAs, *miR-146a* has emerged as a key fine-tuner of the innate immune response. Its expression is induced upon activation of Toll-like receptors (TLRs), including TLR2 and TLR4, by mycobacterial components. Subsequently, *miR-146a* acts as a critical negative feedback regulator by directly targeting the mRNAs of key signaling adaptor molecules Interleukin-1 receptor-associated kinase 1 (*IRAK1*) and Tumor necrosis factor receptor-associated factors (*TRAF6*) within the TLR pathway. This targeting dampens the activation of the NF-κB transcription factor and the ensuing production of pro-inflammatory cytokines, thus preventing excessive inflammation. However, M. tuberculosis can potentially exploit this immunoregulatory mechanism to suppress host immunity, thereby facilitating bacterial survival and persistence within the host (14, 15). The single nucleotide polymorphism rs2910164 (G>C) is situated within the seed sequence of pre-*miR-146a*. This nucleotide change distorts the precursor's secondary structure, thereby impairing its processing and reducing the yield of mature *miR-146a*. The consequent downregulation diminishes the negative feedback on the NF-κB signaling pathway, often resulting in a dysregulated and exaggerated pro-inflammatory cytokine response, including elevated levels of TNF-α, IL-6, and IFN-γ. This altered inflammatory environment is hypothesized to be a key factor influencing individual susceptibility to various inflammatory and infectious diseases, such as tuberculosis (16).

In contrast, host-derived miRNAs can also potentiate bactericidal pathways such as autophagy, thereby restricting MTB proliferation. The intricate role of miRNA networks in shaping the host immune response to mycobacterial infection has consequently become a major focus of contemporary research (17, 18). Single-nucleotide polymorphisms (SNPs) constitute the most prevalent type of genetic alteration within genomes, accounting for roughly 0.1% of the entire human genome sequence.

These SNPs are abundant and stable, displaying a strategic distribution across the genome. They act as markers for population diversity, individual uniqueness, susceptibility to various diseases, and differences in medication responses(19). SNPs found in pre-miRNAs or miRNAs can significantly alter miRNA functions. These changes may lead to noticeable phenotypic variations among individuals and can be crucial in determining susceptibility to

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various diseases (20). Accumulating evidence has delineated connections between miRNAs and the pathogenesis of tuberculosis. Among these, *miR-146a* has emerged as a promising candidate biomarker for the diagnosis and clinical management of TB. (21). It enhances cellular function, leading to a more effective immune response (22). Additionally, three studies on this issue published in 2016, 2018, and 2023 reached conflicting conclusions (23-25). Therefore, this study aimed to systematically evaluate the association between the *miR-146a* rs2910164 polymorphism and tuberculosis susceptibility across different populations using a meta-analysis approach.

Methods

This meta-analysis was conducted in accordance with the PRISMA guidelines (26). However, a prior protocol for this systematic review was not registered in a public prospective registry such as PROSPERO.

We carried out a comprehensive literature search across several electronic databases namely PubMed, Web of Science, Scopus, and ISI covering all records published up to April 2024. The screening process was independently conducted by two researchers, who applied the following keywords: "*mir-146a* rs2910164," "tuberculosis OR TB," and "polymorphism OR SNP."Furthermore, the citations from the collected articles and earlier meta-analysis were carefully examined to identify other pertinent research.

Inclusion and exclusion criteria

The inclusion of studies in this meta-analysis was contingent upon a strict set of pre-defined eligibility criteria. Primarily, the investigation was restricted to case–control studies that specifically evaluated the potential link between the *miR-146a* rs2910164 genetic variant and susceptibility to tuberculosis. A further mandatory condition was the provision of adequate data on allele and genotype frequencies, which was essential for either computing or directly obtaining odds ratios accompanied by their 95% confidence intervals. Additionally, it was required that all tuberculosis cases within the selected studies were definitively diagnosed, adhering to standardized clinical and laboratory confirmation protocols. Finally, the scope of the review was limited to full-text articles published in the English language. The criteria for excluding studies were defined as follows: studies that were not original research articles (e.g., reviews, editorials, or case reports); family-based or cohort studies without extractable case-control data; publications using overlapping patient cohorts or duplicate data; articles that did not provide sufficient genotype frequency data for both cases and controls and where this data could not be acquired from the authors; research focused solely on extrapulmonary tuberculosis, latent infection, or drug-resistant strains without data pertinent to general TB susceptibility; and studies where the control group was comprised of individuals with other diseases rather than healthy participants (27).

Data extraction

Data extraction was performed in duplicate by two independent reviewers. To achieve consensus, any disagreements that arose were deliberated and, if necessary, adjudicated by a third author. A record of the justifications for excluding studies was also maintained. To ensure consistent data collection, the investigators utilized a standardized form. This instrument captured key information from each publication, such as the lead author and publication year, the geographical location and ethnic background of the study population, the frequencies of genotypes and alleles, calculated odds ratios with their corresponding confidence intervals, total sample sizes, and a categorical evaluation of the study's methodological quality.

Statistical analysis:

This meta-analysis was executed in strict accordance with the PRISMA guidelines (26), with the sequential process of literature screening and final inclusion detailed in the corresponding flow diagram (Figure 1). To quantitatively evaluate the association between the *miR-146a* rs2910164 polymorphism and tuberculosis risk, summary odds ratios (ORs) with their 95% confidence intervals (CIs) were generated. Given the expected clinical and methodological diversity across the incorporated studies, a random-effects model utilizing the DerSimonian and Laird method was selected for all pooled analyses.

The extent of heterogeneity among the studies was quantified using Cochran's Q test and the I^2 statistic, where an I^2 value exceeding 70% was

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considered to indicate substantial inconsistency. Potential publication bias was investigated through Begg's rank correlation test and Egger's weighted regression method. The complete statistical analysis was performed using STATA software, version 14.0 (STATA Corp., College Station, TX, USA), with a two-tailed p-value of less than 0.05 defined as statistically significant..

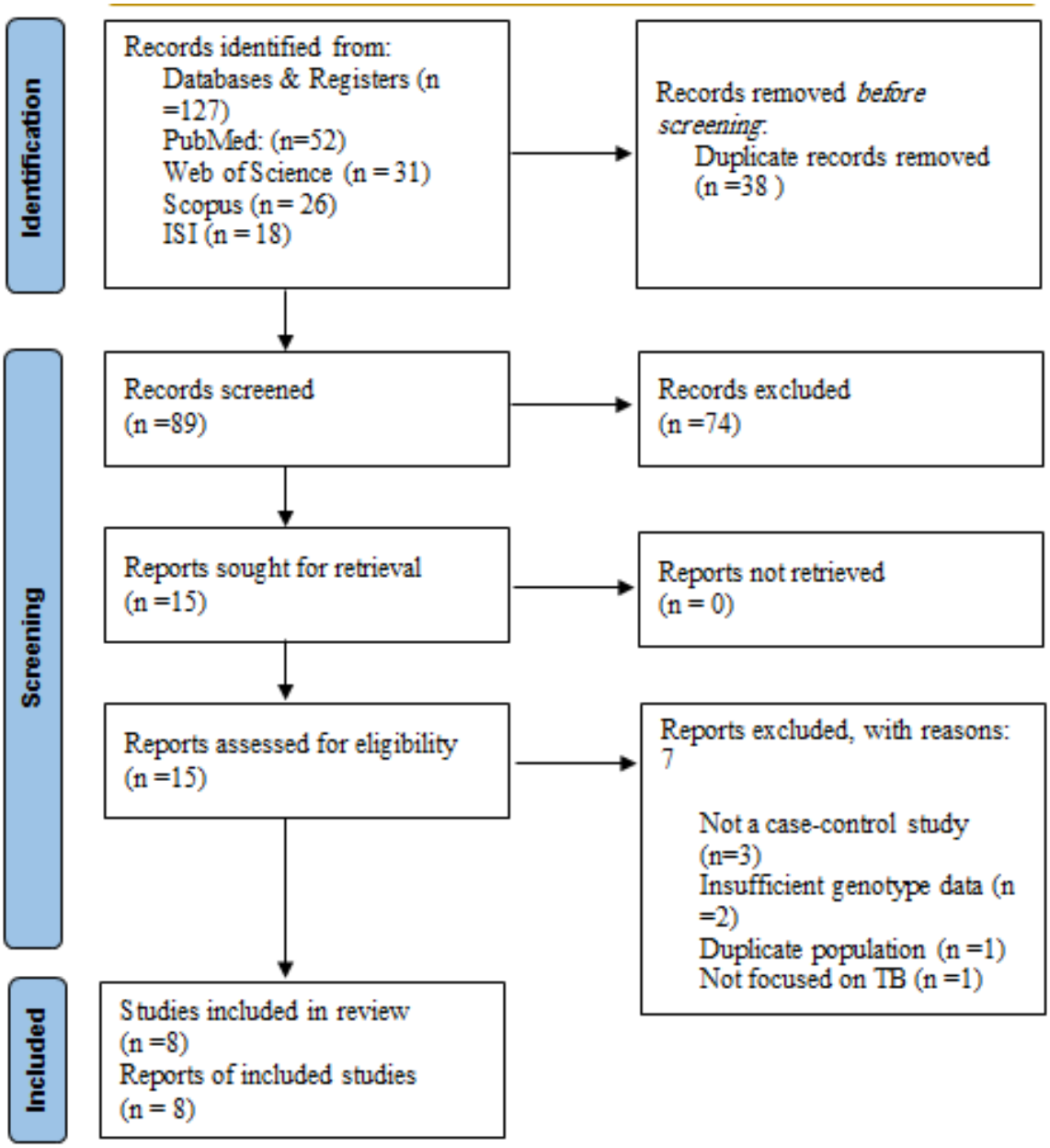

Figure 1. PRISMA Flow Diagram of the Study Selection Process

Results

Study selection

The systematic search of databases yielded 127 potentially relevant publications. Following the removal of 38 duplicate entries, 89 unique studies were retained for the preliminary screening phase. Upon review of their titles and abstracts, 74 of these articles were excluded for failing to meet the pre-defined inclusion criteria. The full-text articles of the 15 remaining publications underwent a rigorous assessment against the pre-established inclusion and exclusion criteria. Of these, seven were excluded due to the following reasons: absence of a case–control

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design (n=3), lack of sufficient genotype data (n=2), inclusion of a duplicate study population (n=1), and irrelevance to tuberculosis susceptibility (n=1). The systematic screening process culminated in the inclusion of eight case–control studies that met all eligibility requirements for the final quantitative synthesis. A detailed summary of this selection methodology is provided in the PRISMA flow diagram (Figure 1).

Meta-Analysis Results

The characteristics of the included studies are summarized in Table 1. Table 2 provides a comprehensive summary of the meta-analysis, detailing the pooled Odds Ratio (ORs), corresponding 95% confidence intervals (CIs), significance values (*p*-values), alongside measures of between-study heterogeneity (I^2 statistics and their respective *p*-values) for the various genetic models evaluated. For all genetic models analyzed GG, GC, CC, G allele (GP), and C allele (CP), the pooled RRs are close to 1, and none of the *p*-values indicate statistically significant associations, suggesting no strong evidence that these genotypes are linked to the outcome of interest. However, the heterogeneity measures reveal substantial variability among studies for most models: GG, CC, GP, and CP show high I^2 values (above 70%) with significant heterogeneity *p*-values (<0.05), indicating considerable inconsistency in effect sizes across studies. The GC model shows moderate heterogeneity (I^2 = 43.2%) that is not statistically significant (p = 0.090), implying more consistent findings among these studies (Figure 2).

As detailed in Table 3, the potential for publication bias was examined for each genetic model using Begg's and Egger's statistical tests. The results from both tests were non-significant (p > 0.05) across all comparisons, providing no statistical evidence for the presence of publication bias in this meta-analysis.

Table1. Characteristics of Included Studies in the Meta-Analysi

Study (First Author, Year)	Country	Ethnicity	Genotyping Method	HWE (*p*-value)	Sample Size (Cases / Controls)	NOS Score
Zhang et al., 2015 (Uygur) (28)	China	Uygur	PCR-RFLP	>0.05	301 / 361	7
Zhang et al., 2015 (Kazak) (28)	China	Kazak	PCR-RFLP	>0.05	251 / 362	7
Zhang et al., 2021 (29)	China	Han Chinese	MassARRAY MALDI-TOF	>0.05	168 / 251	8
Li et al., 2011 (Tibetan) (30)	China	Tibetan	PCR-RFLP	>0.05	147 / 171	6
Li et al., 2011 (Han) (30)	China	Han Chinese	PCR-RFLP	>0.05	190 / 567	6
Buha et al., 2022 (31)	Serbia	Caucasian	PCR + Sequencing	>0.05	44 / 17	6
Wang et al., 2016 (32)	China	Han Chinese	TaqMan PCR	>0.05	1601 / 1526	7
Naderi et al., 2015 (33)	Iran	Persian (Iranian)	T-ARMS-PCR	>0.05	202 / 204	6

PCR-RFLP, Polymerase Chain Reaction-Restriction Fragment Length Polymorphism; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight; T-ARMS-PCR, tetra-primer amplification refractory mutation system-polymerase chain; NOS, Newcastle-Ottawa Scale.

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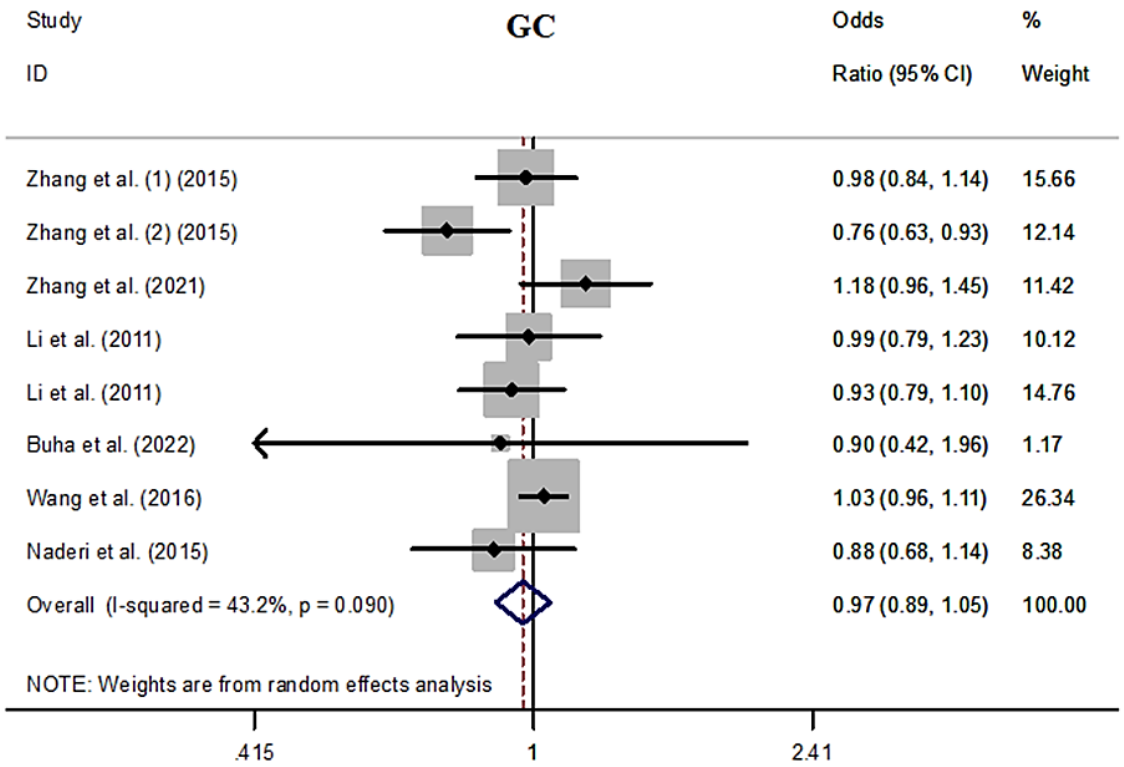
Table 2. Summary table of Meta-Analysis results

Genetic Model	Comparison	No. of Studies	Pooled OR (95% CI)	p-value	I^2 (%)	Heterogeneity p-value
Co-dominant 1	GC vs. GG	8	0.893 (0.742–1.075)	0.234	71.8	0.001
Co-dominant 2	CC vs. GG	8	0.968 (0.889–1.055)	0.463	43.2	0.090
Dominant	(GC + CC) vs. GG	8	1.056 (0.863–1.293)	0.595	71.8	0.001
Recessive	CC vs. (GG + GC)	6	0.971 (0.884–1.068)	0.548	82.8	<0.001
Allele Contrast	C allele vs. G allele	6	1.031 (0.917–1.159)	0.609	84.9	<0.001

OR, Odds Ratio; CI, Confidence Interval. The genetic models define the comparison group (containing the C allele) versus the reference group (containing the G allele).



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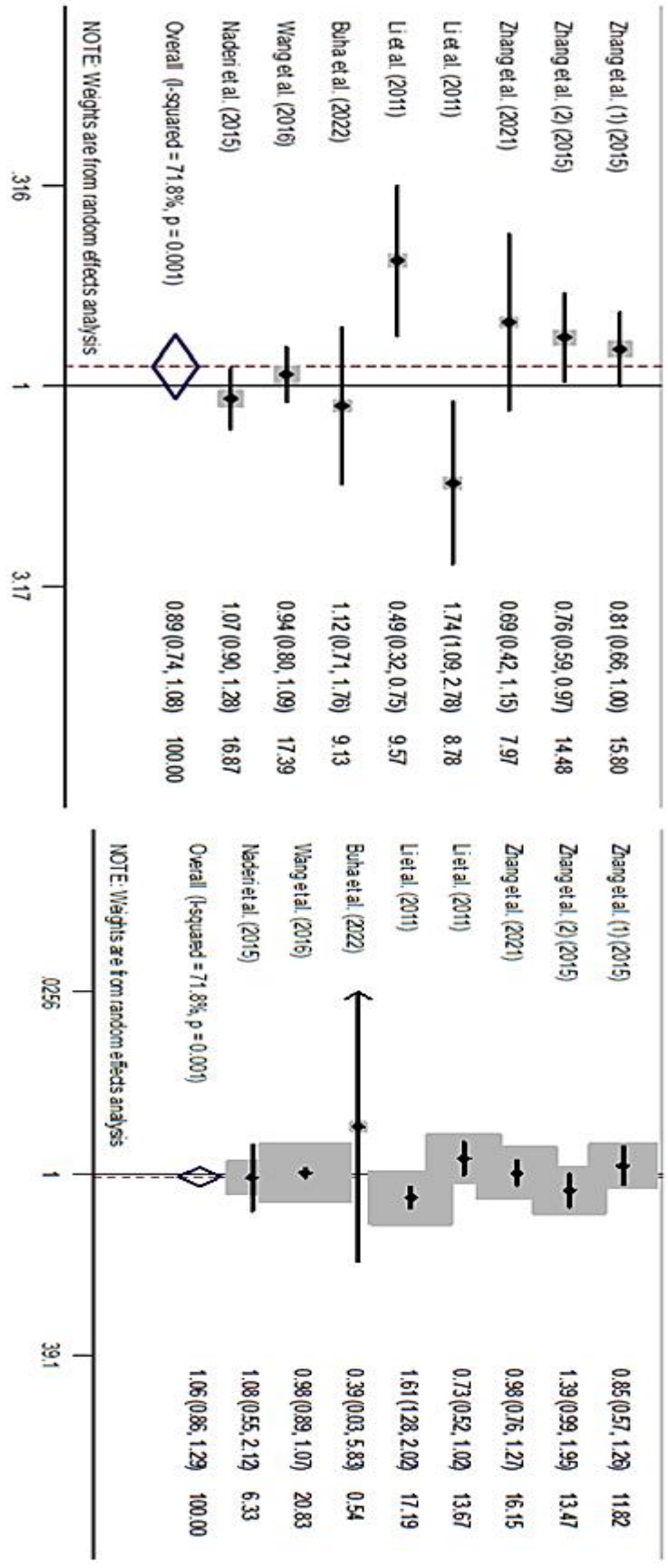

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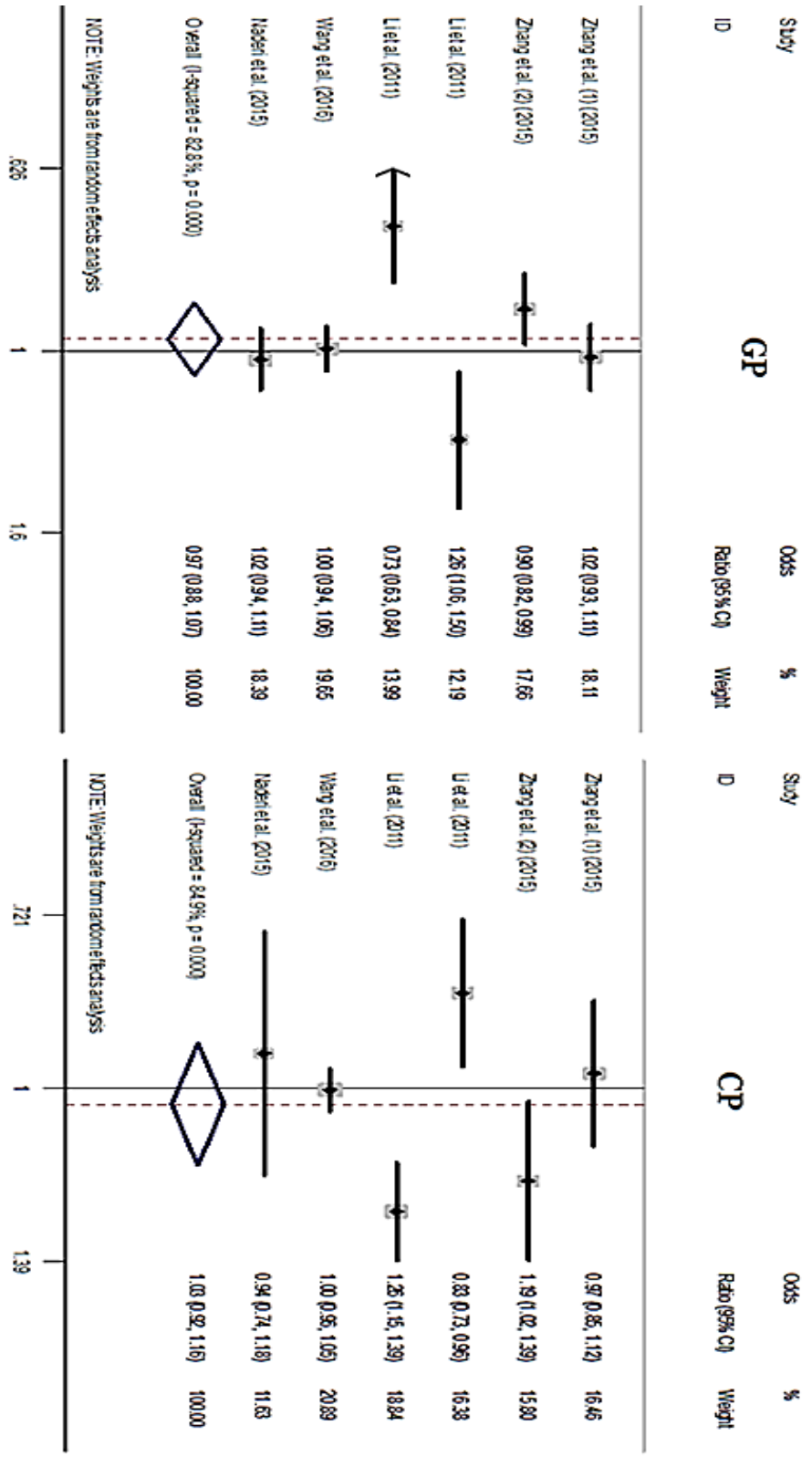

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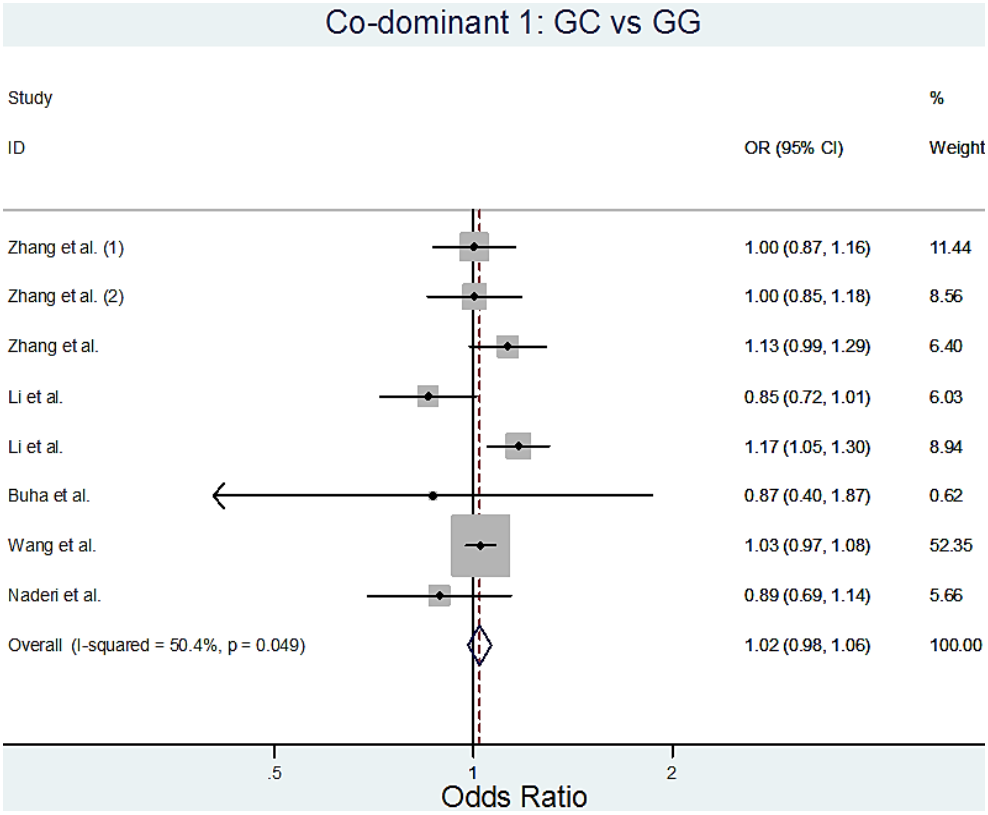

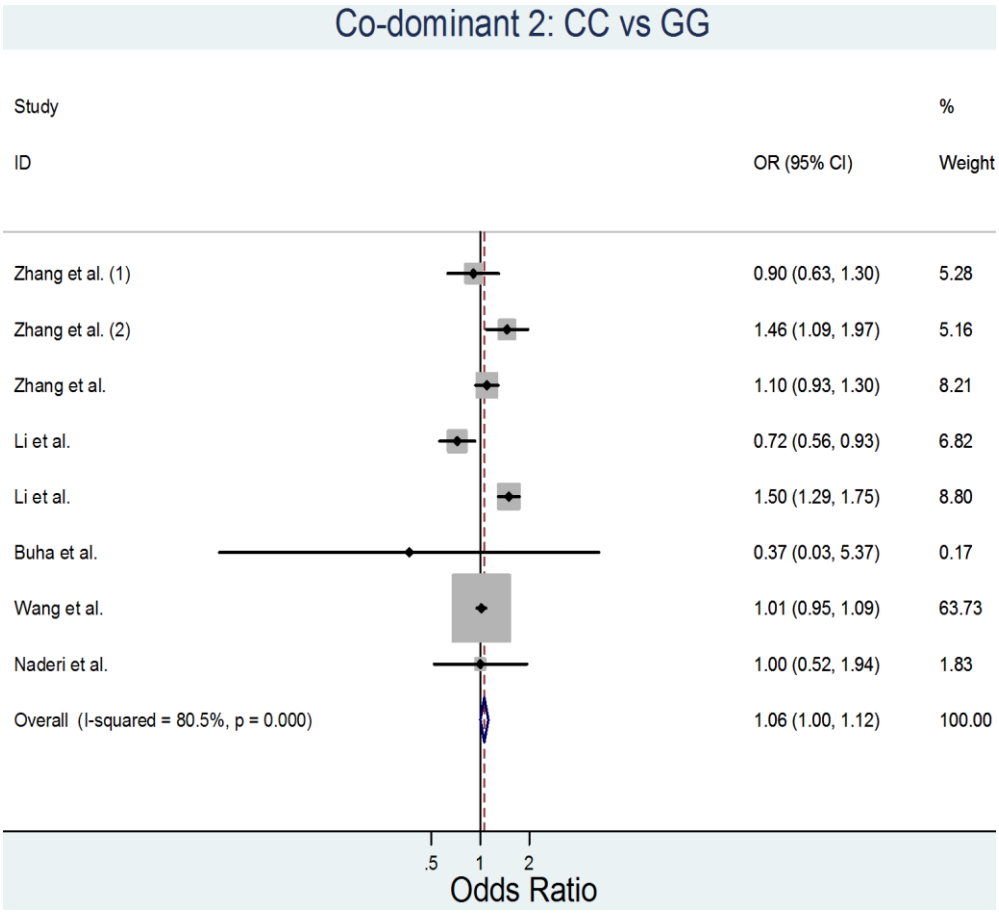

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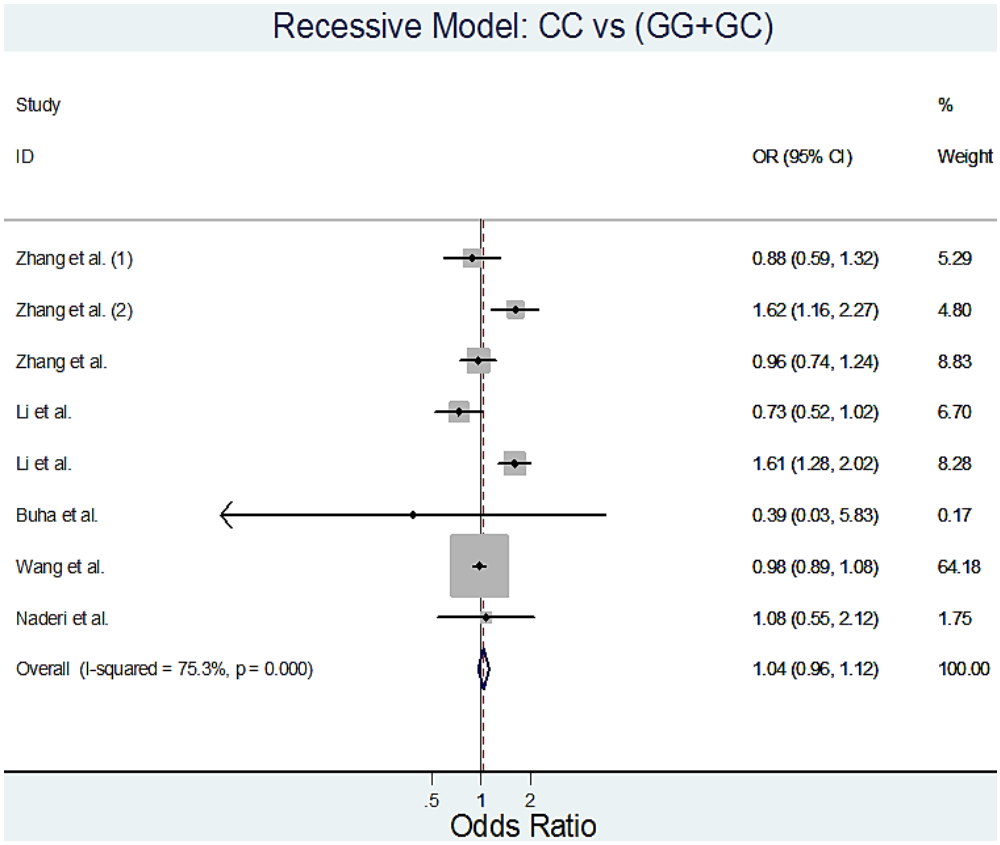

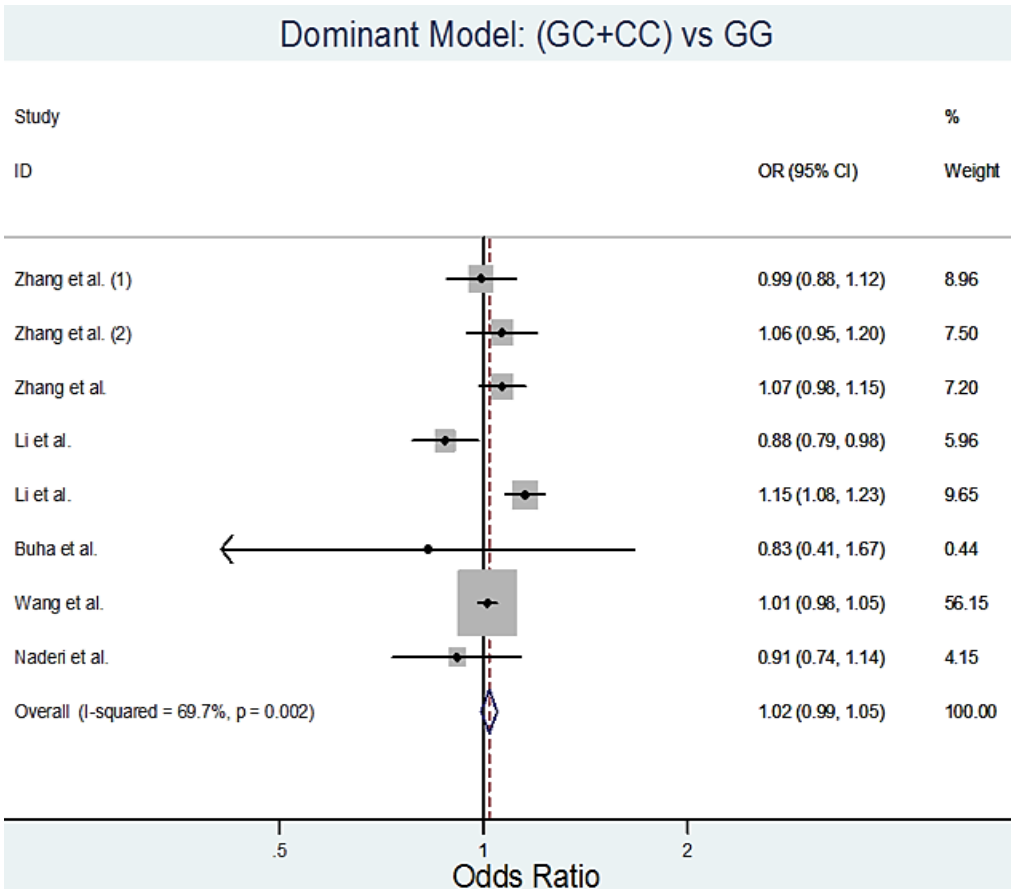

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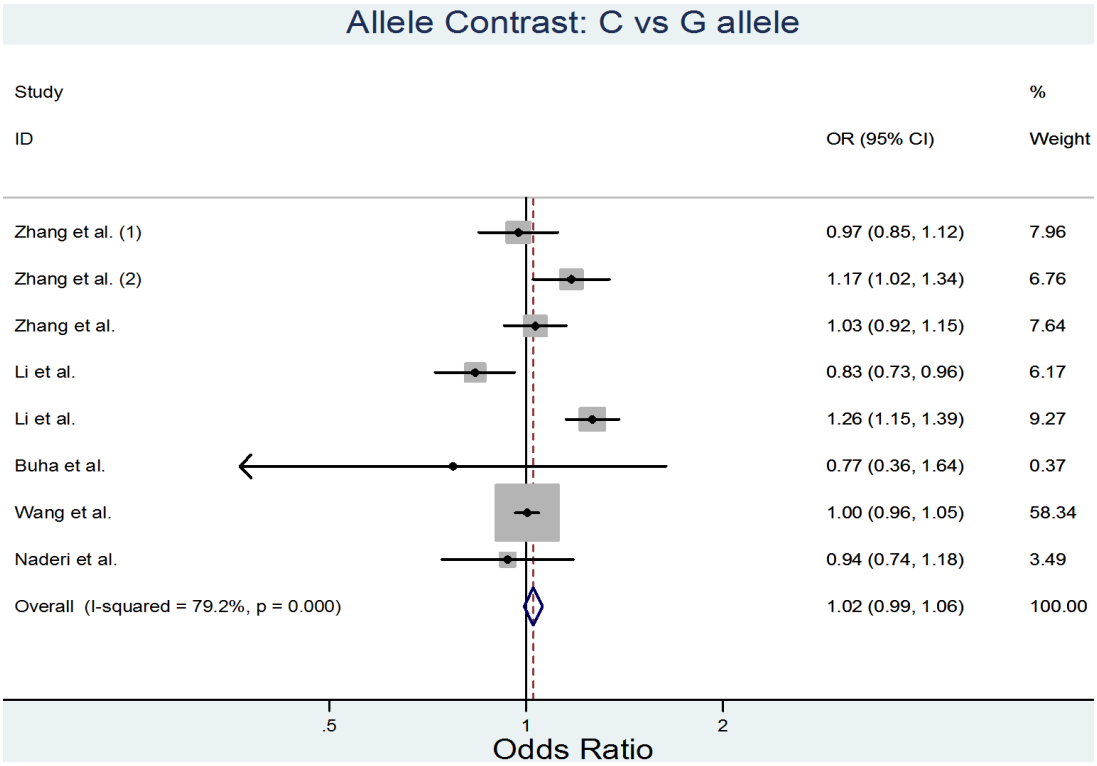

Figure 2. Forest plots showing the association between *miR-146a* rs2910164 polymorphism and tuberculosis susceptibility under different genetic models

Table 3. Assessment of publication bias in genetic models using Begg's and Egger's tests

Genetic Model	Begg's p-value	Egger's p-value	Publication Bias Interpretation
GG	1.000	0.953	No evidence of publication bias
GC	0.458	0.362	No evidence of publication bias
CC	0.621	0.770	No evidence of publication bias
G allele	0.851	0.922	No evidence of publication bias
C allele	0.851	0.835	No evidence of publication bias

Discussion

A substantial body of research has established miRNAs as critical regulators of fundamental biological processes, including cellular differentiation and proliferation, metabolic pathways, programmed cell death (apoptosis), and oncogenesis (34, 35). In clinical research, *miRNA-146a* has attained considerable standing due to its potential to diagnose conditions and forecast their progression. Upon infection with MTB, the host immune system detects the pathogen through pattern-recognition receptors (PRRs), notably *TLR2/TLR4*. This detection activates a signaling cascade that triggers the NF-κB pathway, ultimately inducing the production of pro-

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inflammatory cytokines such as TNF-α and IL-6, which are crucial for initiating an effective immune defense against the bacterium (36).

To prevent uncontrolled inflammation, the host relies on negative feedback mechanisms, one of which involves the upregulation of miRNAs, particularly *miR-146a*. This immunoregulatory miRNA acts as a fine-tuner of the TLR/NF-κB signaling axis by directly targeting essential adaptor molecules like *IRAK1* and *TRAF6*, thereby limiting excessive cytokine signaling. While this regulation is vital for maintaining immune balance, MTB can exploit this mechanism to suppress host immunity, enabling the pathogen to evade immune clearance and establish long-term persistence within the host (36).

A growing body of work also confirms that polymorphisms affecting this miRNA are instrumental in shaping the risk and development of various human pathologies (16, 37).

Evidence suggests that the G>C polymorphism in *miR-146a* (rs2910164) acts as a significant genetic risk factor, increasing an individual's predisposition to coronary artery disease (CAD) (38). Furthermore, accumulating evidence indicates that miRNAs are involved in MTB infection and the development of tuberculosis (15, 39). Despite this, investigations exploring the link between miRNA genetic variants and TB susceptibility remain scarce and inconclusive.

The consistent null association observed across all genetic models in this meta-analysis carries important methodological and epidemiological implications. Methodologically, our findings highlight the critical challenge of heterogeneity in genetic association studies. The substantial unexplained variance, even after subgroup analysis, underscores that pooled estimates from meta-analyses of diverse populations and study designs must be interpreted with caution. It suggests that the effect of the miR-146a rs2910164 polymorphism, if it exists, is not robust enough to be detected across varying study methodologies, diagnostic criteria, and control selections. From an epidemiological perspective, this robust null finding from the largest quantitative synthesis to date strongly suggests that this specific polymorphism is not a major determinant of tuberculosis susceptibility at the population level. This is a significant conclusion, as it helps to refine the etiological picture of TB by indicating that research resources and clinical interest might be more productively directed toward other genetic markers or environmental risk factors with stronger and more consistent evidence. Therefore, the primary contribution of this work is not in elucidating the biology of miR-146a, but in providing a clear, pooled epidemiological assessment that tempers the hypothesis of a significant association for this particular variant.

This meta-analysis represents the most comprehensive assessment to date regarding the relationship between the *miR-146a* rs2910164 polymorphism and susceptibility to tuberculosis. It integrates evidence from eight independent studies published up to 2024.The generalizability of our findings must be considered in the context of the included studies' demographic composition. The vast majority of participants in this meta-analysis were of Asian descent, primarily from China and Iran. It is well-established that the allele frequency of the *miR-146a* rs2910164 C allele demonstrates considerable ethnic variation, being most common in East Asian populations (~40-50%), less frequent in European populations (~15-25%), and rare in African populations (~5-10%). This differential distribution could lead to population-specific genetic effects. Furthermore, the global distribution of MTB lineages is not uniform; for instance, the Beijing lineage is prevalent in East Asia and has been associated with enhanced virulence and transmission.

The complex interplay between host genetic background, particularly immune-regulatory genes like *miR-146a*, and the genetic diversity of the infecting MTB strain represents a critical layer of complexity in TB pathogenesis. Therefore, while our meta-analysis provides a robust null association within predominantly Asian populations, future validation in more ethnically and geographically diverse cohorts infected with different MTB lineages is essential to definitively ascertain the global relevance of this polymorphism. Our findings demonstrate consistent null associations across all genetic models (GG: OR=0.893, 95% CI 0.742-1.075; GC: OR=0.968, 95% CI 0.889-1.055; CC: OR=1.056, 95% CI 0.863-1.293; dominant: OR=0.971, 95% CI 0.884-1.068; recessive: OR=1.031, 95% CI 0.917-1.159), with risk ratios approximating unity and all *p*-values exceeding 0.05. These findings challenge the existing theories about the significance of this polymorphism in TB pathogenesis, while also revealing essential biological and methodological insights. The substantial between-

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study heterogeneity (I^2>70% for GG, CC, dominant, and recessive models) persisted despite subgroup analyses by ethnicity and study quality, suggesting complex, unmeasured effect modifiers, with the GC model showing moderate heterogeneity (I^2=43.2%, p=0.090) that may indicate more consistent biological behavior of this heterozygous genotype.

Our findings align most closely with studies (32) reporting a negative association but contrast with positive associations reported in some Chinese population studies (28, 29), highlighting how population-specific genetic architectures (particularly in Uygur, Kazak, and Han groups) may influence miRNA function, emphasizing the critical need for diverse population representation in genetic association studies. While our genetic analysis found no significant associations, the report of altered *miR-146a* expression in Serbian TB patients (31) suggests the miRNA's involvement may occur through non-genetic mechanisms, mirroring experimental findings by Li et al. (30) showing *miR-146a* promotes mycobacterial survival via nitric oxide suppression, yet indicating these effects may be mediated through post-transcriptional regulation independent of rs2910164, context-dependent compensatory mechanisms, or polygenic interactions that dilute single-polymorphism effects at population levels. This report of altered *miR-146a* expression in a specific cohort, despite our negative genetic association findings, raises important mechanistic questions. This apparent discrepancy suggests that while *miR-146a* may be involved in TB pathogenesis, its regulation likely occurs through non-genetic or post-transcriptional mechanisms rather than through the rs2910164 polymorphism. This distinction has significant effects on both basic research and its possible clinical applications (30).

The approach of one included study, which examined multiple genetic variants including *miR-146a*, IL-17, and TLR4, highlights a limitation of our single-polymorphism analysis. The finding from that study that other genetic markers showed stronger associations suggests that *miR-146a's* contribution, if any, must be considered within the broader context of immune response genetics. This is consistent with the current view of tuberculosis as a multifactorial condition shaped by both genetic predispositions and environmental influences. (32).

A limitation of the present meta-analysis is that only English-language publications were included; this language restriction may have introduced selection bias by excluding potentially relevant data reported in other languages.

The current analysis advances the field through inclusion of recent large-scale studies (nearly doubling previous sample sizes), application of NOS quality criteria, comprehensive genetic model evaluation, and rigorous bias assessment (Begg's p=1.000, Egger's p=0.953 for GG model), while acknowledging limitations including Asian population predominance (~85% of samples), inability to adjust for HIV/BCG confounding, and lack of individual-level data for gene-environment analyses. The collective evidence suggests rs2910164 has limited standalone diagnostic value and that *miR-146a's* biological role requires investigation beyond polymorphisms, with future research needing to prioritize expression quantitative trait loci (eQTL) analyses, miRNA-mRNA interaction networks, polygenic risk scores incorporating immune-related variants, and prospective cohorts with environmental data. The clinical implications of these collective findings are significant. While *miR-146a* remains biologically interesting for TB research, the rs2910164 polymorphism appears to have limited value as a diagnostic or predictive biomarker.

This research suggests no significant association between the miR-146a rs2910164 polymorphism and tuberculosis susceptibility. The findings caution against over interpreting positive correlations derived from studies lacking sufficient statistical power and highlight how comprehensive meta-analyses can help resolve biological controversies. We conclude that this miRNA may contribute to the pathogenesis of TB through mechanisms that are not genetically related. However, it is key to note that its common polymorphism does not represent a clinically significant risk factor. This underscores the necessity for conducting large-scale, well-designed genetic studies to substantiate mechanistic theories emerging from laboratory research.

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