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Review Article

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ApaI and BsmI Genotype Polymorphisms Associated with Vitamin D Receptor and Its Association with Pulmonary Tuberculosis: A Systematic Review and Meta-Analysis

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Abstract

Introduction: The precise effect of vitamin D Receptor (VDR) gene polymorphisms on pulmonary tuberculosis (TB) is still a matter of debate. This research aimed to investigate BsmI and ApaI polymorphisms on the susceptibility to TB.

Methods: VDR gene polymorphism prevalence was considered in cases (people with pulmonary TB and polymorphism of VDR genes) and control (healthy people without pulmonary TB and polymorphism of VDR genes) groups during 2010-2023. The evaluation of the quality of the articles was done with the checklist of Joanna Briggs Institute (JBI) systematic reviews checklist for case-control studies and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020. Data were entered into STATA 14 software. Effect size (ES) for polymorphism prevalence and heterogeneity was evaluated based on the random effect model (95% Confidence interval (CI), $\alpha = 0.05$).

Results: In this review, 17 articles were analyzed. The prevalence of polymorphism between two groups of cases (polymorphism of VDR genes in people with pulmonary TB) and controls (polymorphism of VDR genes in healthy people without pulmonary TB) was different and significant ($P < 0.001$). The highest overall prevalence of polymorphism related to Aa genotypes in the control group (95% CI: 0.34-0.56, ES = 0.45, weight: 49.72) and bb in the case group (95% CI: 0.23-0.66, ES = 0.45, weight: 47.19).

Conclusion: VDR gene polymorphisms were different between the case and control groups. The most important polymorphisms were associated with Aa and bb genotypes. Human populations with polymorphisms of the VDR genes may be more susceptible to pulmonary TB.

Keywords: Genotype, Polymorphisms, Vitamin D Receptor, Tuberculosis

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Introduction

Tuberculosis (TB) is one of the major health problems worldwide, and it often affects the lungs (1). *Mycobacterium tuberculosis* (*M. tuberculosis*) is the cause of this disease, which can remain in the body for a long time without any symptoms. This delay is long-term, without damage and transmission from one person to another; when it is together with other infectious agents in the body of the affected person, it can weaken the immune system (2, 3). The World Health Organization (WHO) reported that Southeast Asia, Africa, India, and China account for the largest number (40%) of TB cases globally (2). According to the WHO, it is estimated that 10.6 million people worldwide will be infected with TB in 2022, which is equivalent to 133 cases per 100,000 population. Among all TB cases, 6.3% were related to people infected with the Human Immunodeficiency Virus (HIV). The most cases of TB in 2022 in the regions under the WHO supervision were detected in Southeast Asia (46%), Africa (23%), Western Pacific (18%), Eastern Mediterranean (8.1%), America (3.1%), and Europe (2.2%), respectively (4). The WHO in 2024 estimated that more than 10 million people are infected with active TB each year, and approximately 1.5 million deaths are attributed to the disease each year (1). Also, the trend of TB in 10 High-Burden Countries (HBCs) showed a continuous increase in cases of the disease, with India and China jointly accounting for nearly 70% of the disease burden (5). According to the results recorded in the Global Burden of Disease (GBD), the incidence rate (rate per 100,000 persons/year) of TB in Iran in 2010 was 14.61, and in 2019, it had decreased to 12.29 (6). Several different genetic and environmental factors control the intracellular survival of this bacterium and compromise the host's immunity. Risk factors in the living environment, such as working in dust, a polluted work environment, poverty, stress, lifestyle, as well as genetic susceptibility and the

effects of some genes in the host, may affect the infection in different people and its prevalence in different communities and races (7-9). The active form of vitamin D (Calcitriol) directly and indirectly affects the activity of immune cells (T and B cells, monocytes, macrophages, dendritic cells, and natural killer (NK) cells). These immune cells play a role in regulating vitamin D receptor (VDR) genes (FokI (rs2228570), ApaI (rs7975232), BsmI (rs1544410), and TaqI (rs731236)). The mentioned immune cells also regulate the expression of the enzyme 1α-hydroxylase (produced by the CYP27B1 gene), which is responsible for the activation of vitamin D precursors to calcitriol. The production of the active metabolite of vitamin D by immune cells is associated with the stimulation of nitric oxide radical secretion; this action increases the ability of these cells to destroy *M. tuberculosis* (3, 10). Therefore, vitamin D plays an important role in the body's innate immune activity, and vitamin D deficiency is associated with the risk of TB. Polymorphism in VDR genes affects the activity of immune cells and contributes to susceptibility to TB (9). VDR genes are located on chromosome 12cen-q12, which can include single-nucleotide polymorphisms (SNPs) in FokI, ApaI, BsmI, and TaqI genes (Figure 1) (11, 12).

Also, a study in China in 2019 reported that polymorphism of the BsmI and TaqI regions associated with VDR was associated with pulmonary TB (13). In research conducted in Iran in 2024, VDR gene polymorphisms showed a significant relationship with susceptibility to pulmonary TB, and significant heterogeneity was observed between polymorphisms. The prevalence of ApaI and BsmI polymorphism was 43% and 39%, respectively (14). In another study in Iran in 2024, it was reported that the prevalence of vitamin D deficiency in people with pulmonary TB was 68.96%, and in the group without pulmonary TB, it was estimated as 51.72%. There was a statistically significant difference between the prevalence of vitamin D deficiency in the population with and without pulmonary TB. Vitamin D deficiency was higher in people with TB than in those without TB (15). A study in Iran in 2024 on 73 patients with pulmonary TB showed that administering vitamin D supplements at a daily dose of 800 international units for 8 weeks significantly increased the patients' serum vitamin D levels after the intervention. Individuals with the FF genotype of the FokI gene polymorphism had a higher chance of responding positively to treatment compared to those with the BsmI, ApaI, and TaqI polymorphisms (16).

According to studies in different populations, there is still no convincing answer for a definite relationship or lack of a definite relationship between polymorphisms of VDR genes and their effect on contracting pulmonary TB. The results are contradictory, and their relationship is still the topic of discussion in scientific societies related to this issue. Therefore, an up-to-date meta-analysis is needed to obtain a more reliable assessment of the association between VDR gene polymorphisms and the risk of TB in global communities. In this study, in the form of a systematic review article and meta-analysis, we investigated the effects of VDR gene polymorphisms in (BB, bb, Bb) BsmI and (AA, aa, Aa) ApaI genes on susceptibility to TB in the world population.

Methods

The studied community

The studies included patients (all ages, male and female, from different regions of the world) who were suffering from (case group) or without (control group) pulmonary TB, but polymorphisms of the VDR genes were present in them. Articles were included in the study during 2010-2023. These articles were considered according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines (https://www.prisma-statement.org/) (Ethical code IR.MUBABOL.REC.1402.004 (13, 14).

Search strategy

The advanced search process was done, punctuation marks were used to separate specific words, and Google (https://www.google.co.uk/) was used to search a site. Search engines included Google: https://www.google.com/ and Yahoo: https://en-maktoob.yahoo.com/?p=us (12, 13).

Boolean operators were used to limit or expand the query or search results. Control Find (Ctrl+F) was used to find specific words on a web page or a portable document format (PDF) file.

It was used to search a network through a laptop or computer system. Articles entered into EndNote. In

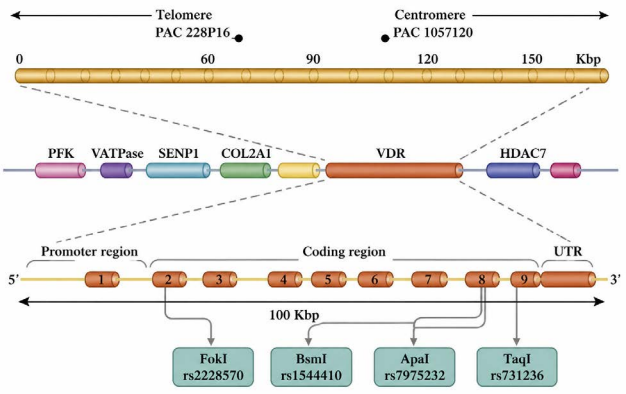

Figure 1. Genomic region and exon/intron structure of the VDR gene. The VDR gene is located on human chromosome 12q13.11 and contains nine exon regions and SNPs, including ApaI (A/a), BsmI (B/b), FokI (F/f), and TaqI (T/t) (12)

Medline, keywords were searched under the title Medical Subject Headings (MeSH). The Search was done in the international databases (Table 1).

Search syntax

Commands and keywords were placed between the script tags. Search syntax is mentioned as an example in the reference database (Figure 2).

List and define all variables

For keyword searches, a precise definition of the participants in the primary studies according to population, intervention, comparator, outcomes, timing, and setting (PICOTS) was presented.

Outline of 4-part questions (PICO)

Description of patient or target population: People with and without pulmonary TB who showed VDR gene polymorphism.

Exposure, intervention, or diagnostic action: Diagnosis of polymorphisms of VDR genes and pulmonary TB by molecular methods was done in people suspected of or suffering from pulmonary TB.

Comparison of intervention or other diagnostic measures: The prevalence of VDR gene polymorphisms was measured in people with or without pulmonary TB.

Outcome: The type and prevalence of polymorphisms of VDR genes in people with or without pulmonary TB were studied during 2010-2023.

Also, authors name, year of study, country, continent, method, average age of patients, genus of patients (female or male), sample size, and polymorphisms related to ApaI (or rs7975232) (genotypes; AA/Aa/aa, alleles; A/a) and BsmI (or rs1544410) (genotypes; BB/Bb/bb, alleles; B/b) were listed and defined as variables.

The main keywords also included the following: vitamin D receptor genes/VDR, polymorphisms, and susceptibility to pulmonary tuberculosis/TB (14).

Inclusion criteria

Articles that investigated the polymorphism of VDR genes BsmI (BB, bb, Bb) and ApaI (AA, aa, Aa) in people with and without pulmonary TB were included in the study. Case-control studies that were conducted on human samples were included in the study (17, 18).

Exclusion criteria

Articles whose only abstracts were available, studies written in languages other than English, articles including meta-analysis, reviews, letters to the editor, abstracts of articles presented in the congress, and articles with an unknown number of samples and lacking the desired information were excluded from the review (14, 18).

In this review, independent studies that had similar variables and focused on the same research question were reviewed, and their information was extracted. So, data extraction from reports was done independently, according to each article. The independent studies were summarized, and the relationships between the variables were examined.

The quality of articles was evaluated using the Joanna Briggs Institute (JBI) and The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [file:///C:/Users/Pascal/Downloads/STROBE-checklist-v4-combined-PlosMedicine.pdf] for case-control studies [https://jbi.global/critical-appraisal-tools].

ES or odds ratio (OR)

In meta-analysis, the OR is a commonly used effect size measure for case-control studies. We aimed to estimate the prevalence of polymorphisms. After extracting the

Table 1. Details of the databases used to search this systematic review and meta-analysis

Databases	URL	Boolean operators	Format	Number of articles searched
Google Scholar	https://scholar.google.com/	AND, OR, and NOT	PDF	55
PubMed	https://pubmed.ncbi.nlm.nih.gov/	AND, OR, and NOT	PDF	49
ScienceDirect	https://www.sciencedirect.com/	AND, OR, and NOT	PDF	10
Scopus	https://www.scopus.com/home.uri	AND, OR, and NOT	PDF	6

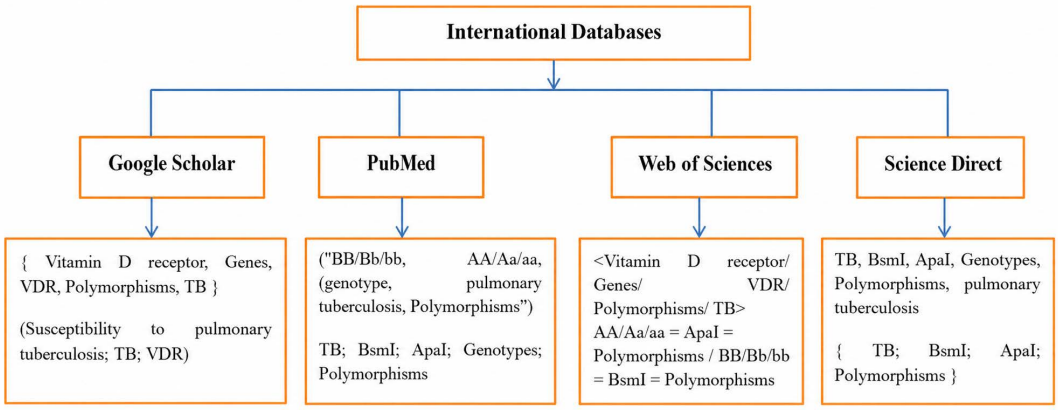

Figure 2. Some examples of search syntax in the reference database

variables from the primary studies, the data were entered into STATA 14 software. In all studies, the weighted average of the indicators in the studies was calculated. Then, heterogeneity was checked using the I2 statistic, and according to the result of this test (heterogeneity greater than 50%), the meta-analysis model was used with weighting by fixed or random effects method (19). Meta-regression and subgroup analysis were performed, but no significant results were obtained to perform subgroup analysis based on a specific variable.

Heterogeneity evaluation method

Heterogeneity refers to the degree of non-uniformity of the results of the studies included in the meta-analysis. The origin of heterogeneity can be clinical, methodological, or a combination of the two. To check this assumption, the Q test (chi-square) was used. If this test was significant, the null hypothesis of the homogeneity of the conducted studies would be rejected, and the hypothesis of heterogeneity among the studies would be confirmed. In other words, the significance of the Q index ($P<0.10$) indicated the existence of heterogeneity in the effect size (ES) or prevalence of primary research. Q index was sensitive to the increase in the number of ES, and with the increase in the number of effects ES, the power of this test to reject homogeneity increased, and the I-squared was another index that was used for this purpose. The squared coefficient of I had a value from zero to 100% and showed the amount of heterogeneity as a percentage. The closer this value to 100%, the higher the heterogeneity of the ES of the primary research. Also, heterogeneity ($\alpha=0.05$) was checked using a forest plot and paying attention to the degree of overlap of the confidence interval (CI) of the target index in different studies. The significant non-overlapping of the CI in different studies was itself proof of the existence of statistical heterogeneity among the studies (14).

The Method of finding the causes of heterogeneity

To find the reasons for the heterogeneity among the studies, the analysis was performed in subgroup analysis and meta-regression subgroups. In the case of heterogeneity, meta-analysis was performed using methods based on random effects (14, 18). Potential benefits of systematic review and meta-analysis include improved precision and the ability to answer questions that are not addressed by individual studies, and resolving discrepancies arising from conflicting results from different studies. Systematic review and meta-analysis take into account estimated random effects of variation between the results of different studies in calculating a weighted average, providing an estimate of the average results of all studies (combining studies appropriately or combining data from multiple studies) (20).

Publication bias evaluation method

The evaluation of publication bias employed various methods, including the Funnel Plot, Begg's, and Egger's tests (19).

Sensitivity analysis method

Sensitivity analysis was done using the cross-validation and trim-and-fill method. Therefore, the stability of the results was maintained when biases and analyses were performed under different conditions and with different statistical methods (18, 21).

Therapeutic intervention, exposure, or diagnostic method

Considering that it was a review study, there was no therapeutic intervention, exposure, diagnostic method, comparison, or outcome. Analysis based on subgroups of existing variables, including age, gender, continent, diagnostic method, polymorph gene, and time range, was considered (18).

Critical appraisal conducted by reviewers

Evaluation of the quality of the included studies and various aspects of the study (relevance, validity, bias, study design, and data analysis), and also interpretation of the results were done by reviewers. JBI critical appraisal tools for use in systematic reviews checklist case-control studies, and the PRISMA 2020 checklist were available to aid reviewers in conducting a critical appraisal. The search for studies was conducted by two co-searchers. Similar articles were removed. Selection of studies, separation based on title, abstract, or full text of articles, and data extraction were done independently by two reviewers. Then, if there was a conflict between the two reviewers in the first stage of discussion and consultation, and in case of disagreement, the opinion of the third reviewer would be used as the criterion. Critical evaluation of the studies was done by three critics more related to the subject (14).

Results

Search Results

Criticism, optimal use of research findings, and reporting of research results were performed using the STROBE checklist. The checklist was completed for all searched articles. Of the 120 searched articles (Figure 3), 17 (14.16%) articles met the criteria for full inclusion in the study and analysis based on the STROBE checklist. Each article was included in the case (Table 2) and control (Table 3) groups (22-24, 3, 25-27).

Relationship between the prevalence of genotype polymorphism of VDR

The prevalence of polymorphism between two groups of cases (people with pulmonary TB and polymorphism of VDR genes) and controls (healthy people without pulmonary TB and polymorphism of VDR genes) was different and significant ($P<0.001$). Also, heterogeneity between studies based on I^2 (%) in each group and overall was high (I^2 close to 100%, $P<0.001$). There is no publication bias in our study ($P>0.05$) (Table 4).

Prevalence of genotype polymorphism of VDR

In this study, the highest prevalence of polymorphisms of VDR-related genes in the case group was associated

Table 2. Information on the articles searched in the databases according to the inclusion and exclusion criteria (case group sample size = 3364)

Articles	Authors	Year	Country	Continent	Method	Age Average	Female	Male	Sample Size	AA	Aa	aa	BB	Bb	bb
(22)	Sari et al.	2022	Indonesia	Asia	SNP genotyping- Real-Time PCR	18-60	96	80	176				103	1	0
(23)	Marashian et al.	2010	Iran	Asia	PCR-RFLP	-	79	85	164	93	51	20	23	86	55
(24)	Yu et al.	2023	China	Asia	Multiplex PCR- sequencing	-	109	112	221	269					
(3)	Rashedi et al.	2013	Iran	Asia	PCR-RFLP				84	29	4	13	27	27	30
(25)	Kang et al.	2011	Korea	Asia	PCR-RFLP	17-69	66	89	155				2	13	235
(26)	Alexandra et al.	2013	Romania	Europe	ARMS	-	15	53	68	19	49	0			
(27)	Salimi et al.	2015	Iran	Asia	PCR-RFLP	51	75	45	120				31	66	23
(28)	Rathored et al.	2012	India	Asia	PCR-RFLP	28	221	471	692				192	346	234
(29)	Lee et al.	2016	Taiwan	Asia	TaqMan SNP genotyping assays	55	61	137	198	186	-	-	-	-	-
(30)	Silva-Ramírez et al.	2019	Mexic	Americas	Real-Time PCR	45	90	167	257	8					
(31)	Zhang et al.	2023	Indonesia	Asia	PCR-RFLP				32	26					
(32)	Sibuea et al.	2022	China	Asia	PCR-RFLP		298	433	731	46					
(33)	Joshi et al.	2014	India	Asia	PCR-RFLP	23	68	42	110				35	58	128
(34)	Ates et al.	2011	Turkey	Asia	PCR-RFLP	47.8	48	80	128				28	68	32
(35)	Harishankar and Selvaraj	2017	India	Asia	PCR-RFLP	39.7			50	11					
(36)	Siregar and Sinaga	2017	Indonesia	Asia	PCR-RFLP		23	53	76	8	33	35	0	52	24
(37)	Fernández-Mestre et al.	2015	Venezuela	Americas	PCR-RFLP	17-70	77	25	102	29	54	18			

Abbreviations: PCR, Polymerase chain reaction; RFLP, Restriction fragment length polymorphism; ARMS, Amplification Refractory Mutation System - Polymerase Chain Reaction; SNP, Single nucleotide polymorphisms, Genotypes; AA allele/Aa allele/aa allele (ApaI gene), Genotypes; BB allele/Bb allele/bb allele (BsmI gene)

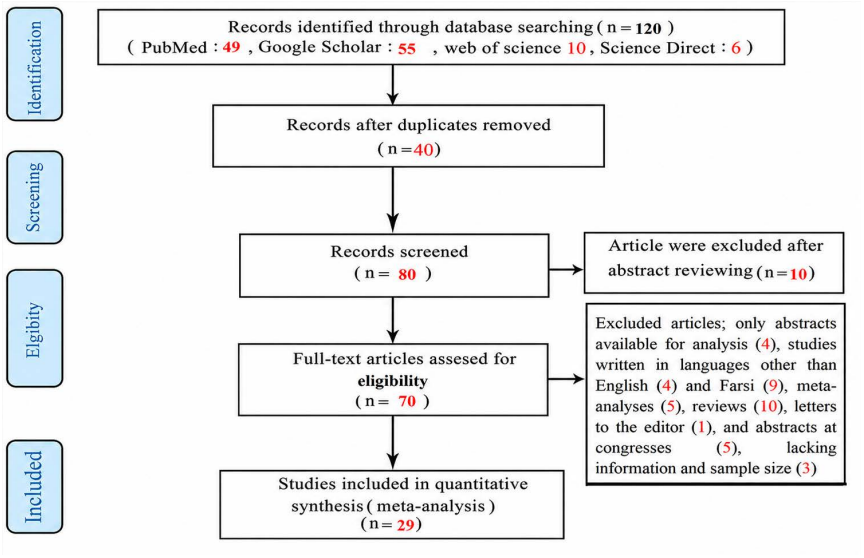

Figure 3. Articles were searched in the databases according to the inclusion and exclusion criteria

with the alleles: bb (0.45 = 45%), AA, and Aa (each one 0.42 = 42%), Bb (0.41 = 41%), BB (0.26 = 26%), and aa (0.22 = 22%), respectively. The highest prevalence of polymorphisms in the control group was identified in the alleles: Aa (0.45 = 45%), Bb (0.4 = 40%), and bb (0.37 = 37%), AA (0.32 = 32%), BB (0.24 = 24%), and aa (0.22 = 22%), respectively. Therefore, the highest polymorphism was observed in the bb allele in the case group, the Aa allele in the control group, and the lowest in the aa allele in both groups (Figure 4).

Prevalence of the AA genotype polymorphism

Heterogeneity assessment detected heterogeneity between the ES in the case ($P < 0.001$, $I^{2**} = 99.91\%$), control ($P < 0.001$, $I^{2**} = 99.21\%$), and all studies ($P < 0.001$, I^2** = 99.87%; Overall). Therefore, meta-analysis was performed using methods based on random effects ($P < 0.001$). In the case and control groups, the highest prevalence was observed in the study performed by Yu et al. (China, 2023) (CI 95%: 0.97-1.00, ES = 0.99, weight: 4.80) (24), and Lee et al. (Taiwan, 2016) (CI 95%: 0.82-0.92, ES = 0.88, weight: 4.79) (29). The lowest prevalence in both cases (CI 95%: 0.02-0.06, ES = 0.03, weight: 4.80) and control (CI 95%: 0.02-0.06, ES = 0.04, weight: 4.80) groups was related to Silva-Ramírez et al. (Mexico, 2019) (30). The overall prevalence associated with AA genotype

Table 3. Information on the articles searched in the databases according to the inclusion and exclusion criteria (control group sample size = 2344)

Articles	Authors	Year of Study	Country	Continent	Method	Age Average	Female	Male	Sample Size	AA	Aa	aa	BB	Bb	bb
(22)	Sari et al.	2022	Indonesia	Asia	SNP genotyping-Real-Time PCR	18-60	96	80	176				46	80	2
(23)	Marashian et al.	2010	Iran	Asia	PCR-RFLP		28	22	50	32	11	7	0	29	21
(24)	Yu et al.	2023	China	Asia	Multiplex PCR-sequencing		251	112	363	459					
(3)	Rashedi et al.	2013	Iran	Asia	PCR-RFLP				90	30	48	12	26	31	33
(25)	Kang et al.	2011	Korea	Asia	PCR-RFLP	21-52	38	67	105				0	8	75
(26)	Alexandra et al.	2013	Romania	Europe	ARMS		54	56	110	27	58	25			
(27)	Salimi et al.	2015	Iran	Asia	PCR-RFLP	48	93	38	121				39	70	22
(28)	Rathored et al.	2012	India	Asia	PCR-RFLP	29	65	140	205				51	108	46
(29)	Lee et al.	2016	Taiwan	Asia	TaqMan SNP genotyping assays	55	91	79	170	149					
(30)	Silva-Ramírez et al.	2019	Mexic	Americas	Real-Time PCR	36	140	317	457	16					
(31)	Zhang et al.	2023	Indonesia	Asia	PCR-RFLP										
(32)	Sibuea et al.	2023	Indonesia	Asia	PCR-RFLP				32	18					
(33)	Joshi et al.	2014	India	Asia	PCR-RFLP	21	30	85	115				55	37	23
(34)	Ates et al.	2011	Turkey	Asia	PCR-RFLP	54.1	30	50	80				5	38	37
(35)	Harishankar and Selvaraj	2017	India	Asia	PCR-RFLP	30.4			60	6					
(36)	Siregar and Sinaga	2017	Indonesia	Asia	PCR-RFLP		23	53	76	8	34	34	2	18	56
(37)	Fernández-Mestre et al.	2015	Venezuela	Americas	PCR-RFLP	26-67	77	25	102	29	54	18			

Abbreviations: PCR, Polymerase chain reaction; RFLP, Restriction fragment length polymorphism; ARMS, Amplification Refractory Mutation System - Polymerase Chain Reaction; SNP, Single nucleotide polymorphisms, Genotypes; AA allele/Aa allele/aa allele (ApaI gene), Genotypes; BB allele/Bb allele/bb allele (BsmI gene)

Table 4. The relationship between the prevalence of genotype polymorphism of VDR genes between two groups of cases (people with pulmonary TB) and controls (people without pulmonary TB)

Polymorphism		Pooled estimate (ES)	Confidence interval (CI)		*P*-value	odds ratio (OR)	(%) I^2	*P*-value	Model	Publication bias
			Maximum	Minimum						(*P*-value)
	Case	0.26	0.13	0.40	<0.001	1.30	98.40	<0.001		
BB	Control	0.24	0.12	0.36	<0.001	1.27	96.10	<0.001	Random effect	0.066
	Overall	0.25	0.17	0.34	<0.001	1.28	97.70	<0.001		
	Case	0.41	0.21	0.61	<0.001	1.51	99.40	<0.001		
Bb	Control	0.40	0.26	0.53	<0.001	1.49	95.80	<0.001	Random effect	0.97
	Overall	0.41	0.27	0.54	<0.001	1.51	99.30	<0.001		
	Case	0.45	0.23	0.66	<0.001	1.57	98.90	<0.001		
bb	Control	0.37	0.19	0.55	<0.001	1.45	98.60	<0.001	Random effect	0.711
	Overall	0.41	0.24	0.57	<0.001	1.51	98.30	<0.001		
	Case	0.42	0.10	0.75	<0.001	1.52	98.90	<0.001		
AA	Control	0.32	0.15	0.49	<0.001	1.38	98.20	<0.001	Random effect	0.589
	Overall	0.38	0.16	0.59	<0.001	1.46	98.90	<0.001		
	Case	0.42	0.16	0.67	<0.001	1.52	98.10	<0.001		
Aa	Control	0.45	0.34	0.56	<0.001	1.57	92.36	<0.001	Random effect	0.929
	Overall	0.43	0.28	0.59	<0.001	1.54	96.80	<0.001		
	Case	0.22	0.11	0.34	<0.001	1.25	89.90	<0.001		
aa	Control	0.22	0.13	0.31	<0.001	1.25	83.70	<0.001	Random effect	0.061
	Overall	0.22	0.15	0.29	<0.001	1.25	85.50	<0.001		

Genotypes; BB allele/Bb allele/bb allele (BsmI gene), Genotypes; AA allele/Aa allele/aa allele (ApaI gene), I^2 index; Substantial bias when the number of studies is small

polymorphism in the case group (95% CI: 0.75-0.10, ES = 0.42, weight: 52.42) was higher than in the control group (95% CI: 0.49-0.15, ES = 0.32, weight: 47.58) (Figure 5).

Prevalence of the Aa genotype polymorphism

A heterogeneity between the ES in the case ($P < 0.001$, I^2** = 98.06%), control groups ($P < 0.001$, I^2** = 82.36%), and all studies ($P < 0.001$, I^2** = 96.82%; Overall).

Therefore, a random effects model was performed ($P<0.001$). The highest and lowest prevalence of Aa polymorphism in the case group was related to Alexandra et al. (Romania, 2013) (CI 95%: 0.81-0.60, ES = 0.72, weight: 9.92) (26) and Rashedi et al. (Iran, 2013) (95% CI: 0.02-0.012, ES = 0.05, weight: 10.32) (3), respectively. In the control group, the highest prevalence of this genotype polymorphism was related to the studies conducted by Rashedi et al. (Iran, 2013) (CI 95%: 0.43-0.63, ES = 0.53, weight: 9.95) (3), Alexandra et al. (Romania, 2013) (95% CI: 0.43-0.62, ES = 0.53, weight: 10.03) (26), and Fernández-Mestre et al. (Venezuela, 2015) 95% CI: 0.62-0.43, ES = 0.53, weight: 10.00), respectively (37). The lowest rate was also reported by Marashian et al. (Iran, 2010) (CI 95%: 0.13-0.35, ES = 0.22, weight: 9.85) (23). The overall prevalence associated with Aa genotype polymorphism in the control group (95% CI: 0.34-0.56, ES = 0.45, weight: 49.72) was higher than that in the case group (95% CI: 0.16-0.67, ES = 0.42, weight: 50.28) (Figure 6).

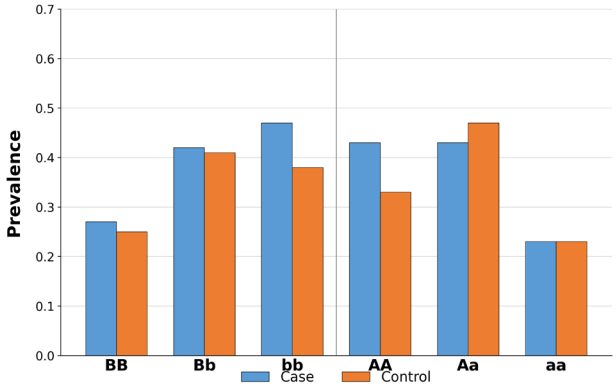

Figure 4. Prevalence (ES) of polymorphism in two groups of cases and controls [Genotypes; BB allele/Bb allele/bb allele (BsmI gene), Genotypes; AA allele/Aa allele/aa allele (ApaI gene)]

Prevalence of the aa genotype polymorphism

Considering the data related to the aa genotype, heterogeneity was observed between the ES in the case ($P<0.001$, I^2** = 89.90%) and control groups ($P<0.001$, I^2** = 83.75%), and all studies ($P<0.001$, I^2** = 49.85%; Overall), a meta-analysis was performed with methods based on random effects ($P<0.001$). The highest prevalence rate associated with aa polymorphism in the case group (95% CI: 0.35-0.57, ES = 0.46, weight: 9.85) and control group (95% CI: 0.34-0.56, ES = 0.45, weight: 9.86) was related to Siregar and Sinaga (Indonesia, 2017) (36). The study of Marashian et al. (Iran, 2010) (CI 95%: 0.08-0.18, ES = 0.12, weight: 12.44) (23) in the case group and Rashedi et al. (Iran, 2013) (CI 95%: 0.08-0.22, ES = 0.13, weight: 11.70) (3) in the control group, evaluated the lowest prevalence associated with aa genotype polymorphism. Also, there was an equal overall prevalence associated with the aa genotype polymorphism in the case group (95% CI: 0.11-0.34, ES = 0.22, weight: 44.96) and control group (95% CI: 0.13-0.31, ES = 0.22, weight: 55.04) (Figure 7).

Prevalence of the BB genotype polymorphism

Regarding the BB genotype, there was heterogeneity between both case ($P<0.001$, I^2** = 98.40%) and control ($P<0.001$, I^2** = 96.06%) groups, as well as all studies ($P<0.001$, I^2** = 97.66%; Overall), therefore, a meta-analysis was performed with the random effect method

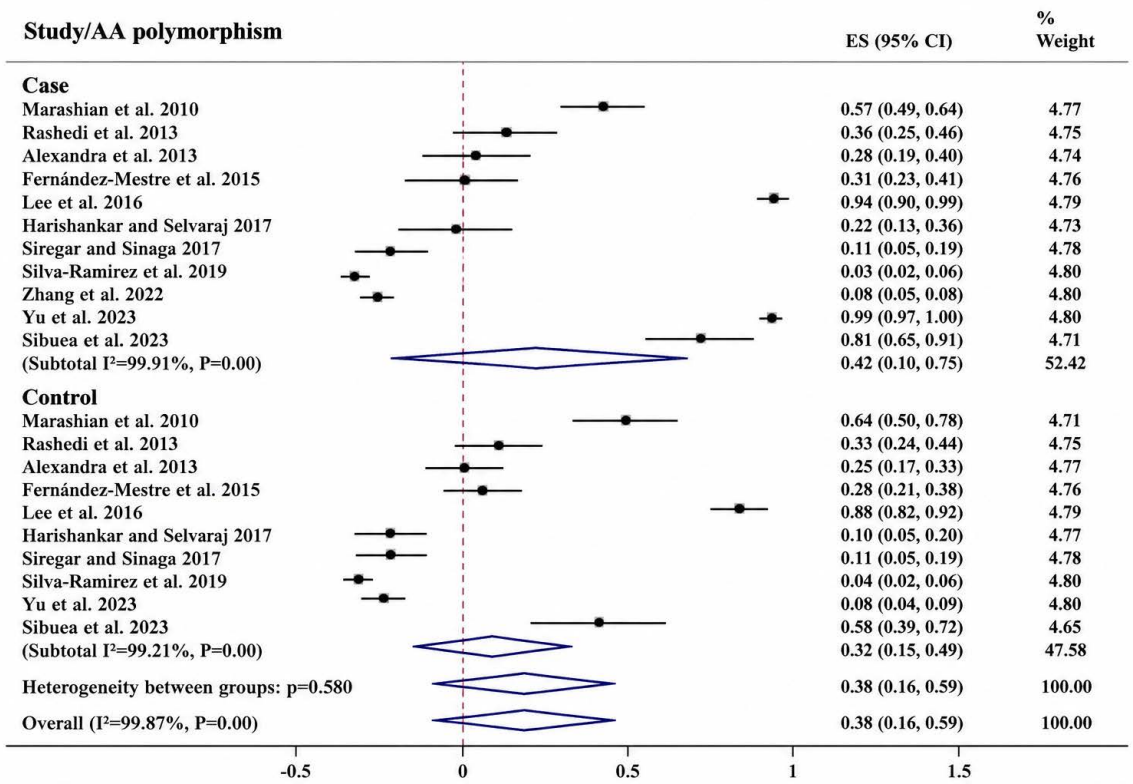

Figure 5. Studies evaluated based on the random effect model in the case and control groups (Study/AA polymorphism). Effect size: ES

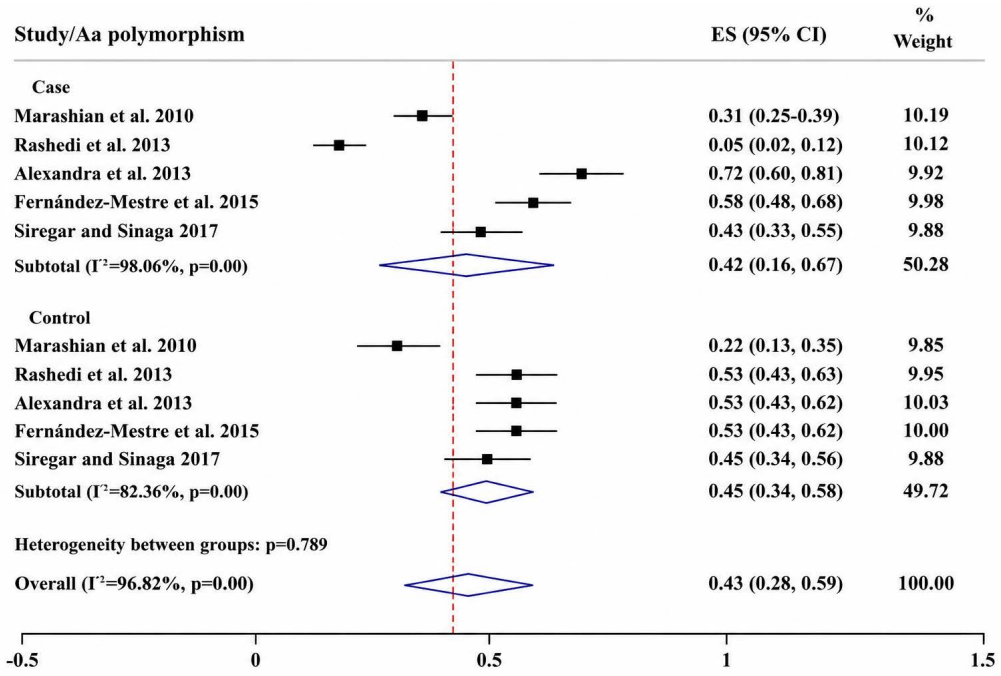

Figure 6. Studies evaluated based on the random effect model in the case and control groups (Study/Aa polymorphism). Effect size: ES

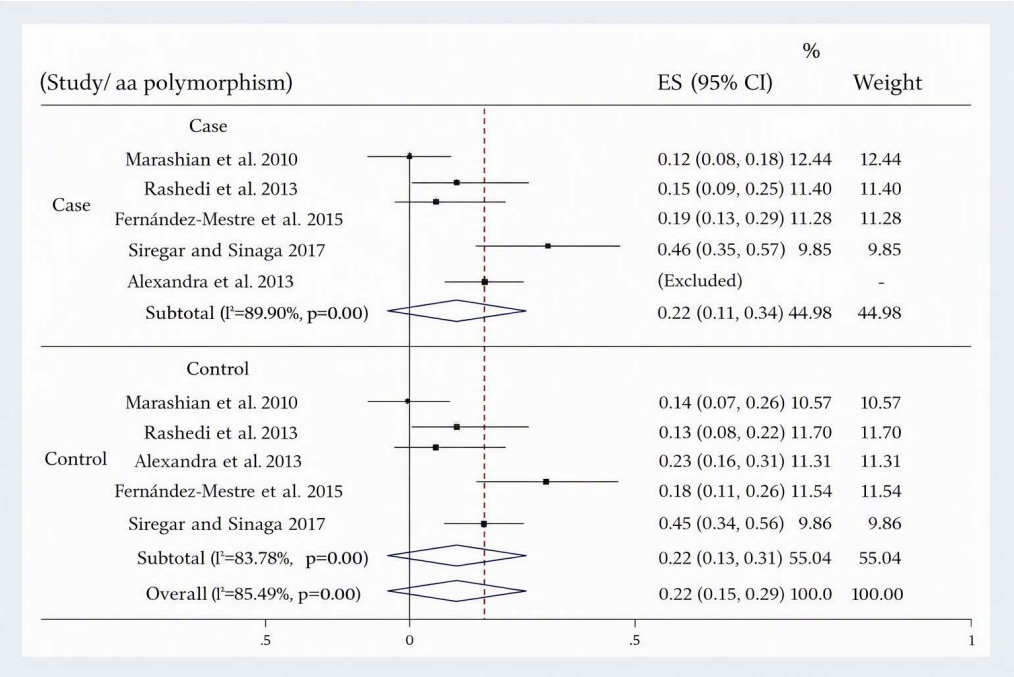

Figure 7. Studies evaluated based on the random effect model in the case and control groups (Study/aa polymorphism). Effect size: ES

($P < 0.001$). In the case group, the highest and lowest prevalence rates related to BB polymorphism were shown in the studies by Sari et al. (Indonesia, 2022) (CI 95%: 0.51-0.66, ES = 0.59, weight: 6.64) (22) and Kang et al. (Korea, 2011) (95% CI: 0.00-0.05, ES = 0.01, weight: 6.96) (25). In the control group, the highest prevalence was related to the research conducted by Joshi et al. (India, 2014) (CI 95%: 0.39-0.57, ES = 0.48, weight: 6.46) (33). The lowest prevalence was observed by Siregar and Sinaga (Indonesia, 2017) (CI 95%: 0.01-0.09, ES = 0.03, weight: 6.89) (36). The overall prevalence associated with the BB genotype polymorphism in the case group (95% CI: 0.13-0.40, ES = 0.26, weight: 53.41) was higher than in the control group (95% CI: 0.12-0.36, ES = 0.25, weight: 46.59) (Figure 8).

The prevalence of the Bb genotype polymorphism

Heterogeneity between cases ($P < 0.001$, I^2** = 99.36%) and controls ($P < 0.001$, I^2** = 95.84%), as well as the total data ($P < 0.001$, I^2** = 99.03%; Overall), was considered using random effects ($P < 0.001$). In the case group, Siregar and Sinaga (Indonesia, 2017) (CI 95%: 0.78-0.57, ES = 0.68, weight: 5.49) (36) and Sari et al. (Indonesia, 2022) (CI 95%: 0.00-0.03, ES = 0.01, weight: 5.69) (22) showed the lowest and highest prevalence associated with Bb polymorphism, respectively. In the control group, Marashian et al. (Iran,

2015) (CI 95%: 0.49-0.66, ES = 0.58, weight: 5.55) (23) and Kang et al. (Korea, 2011) (CI 95%: 0.04-0.14, ES = 0.08, weight: 5.64) (25) showed the highest and lowest prevalence rates of polymorphism in this genotype. The overall prevalence in the case group (95% CI: 0.21-0.61, ES = 0.41, weight: 50.20) was higher than in the control group (95% CI: 0.26-0.53, ES = 0.40, weight: 49.80) (Figure 9).

Prevalence of the bb genotype polymorphism

The random effects method was also used for the analysis of the bb genotype polymorphism ($P < 0.001$). Heterogeneity was observed between case ($P < 0.001$, I^2** = 98.97%), control ($P < 0.001$, I^2** = 98.65%), and overall data ($P < 0.001$, I^2** = 99.31%). In the case group, the highest and lowest prevalence rates associated with the

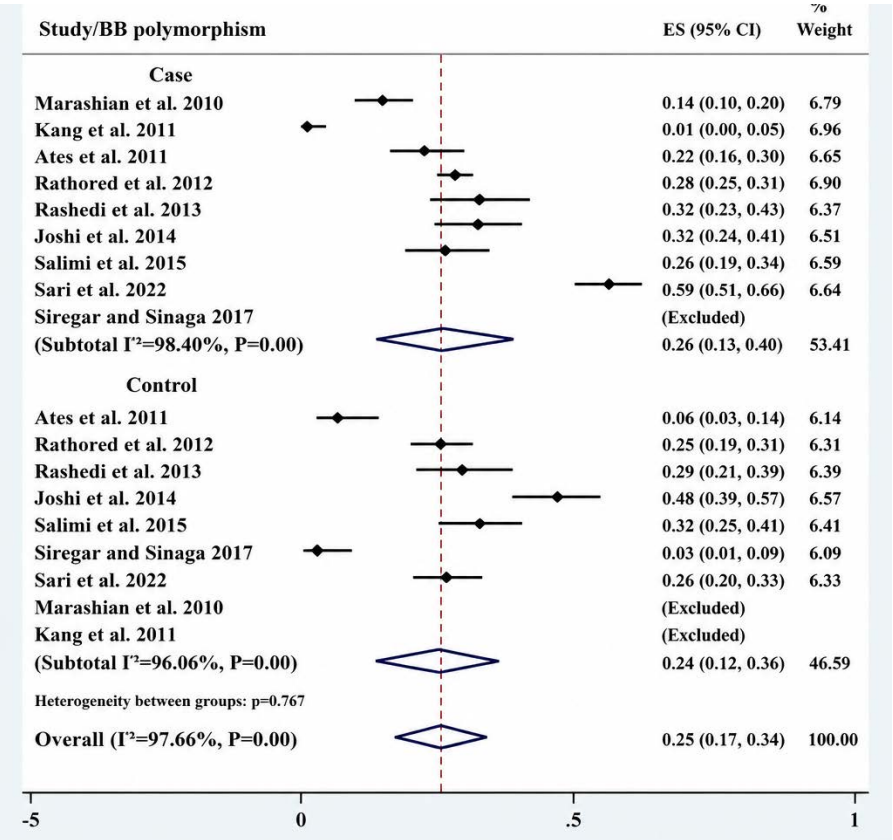

Figure 8. Studies evaluated based on the random effect model in the case and control groups (Study/BB polymorphism). Effect size: ES

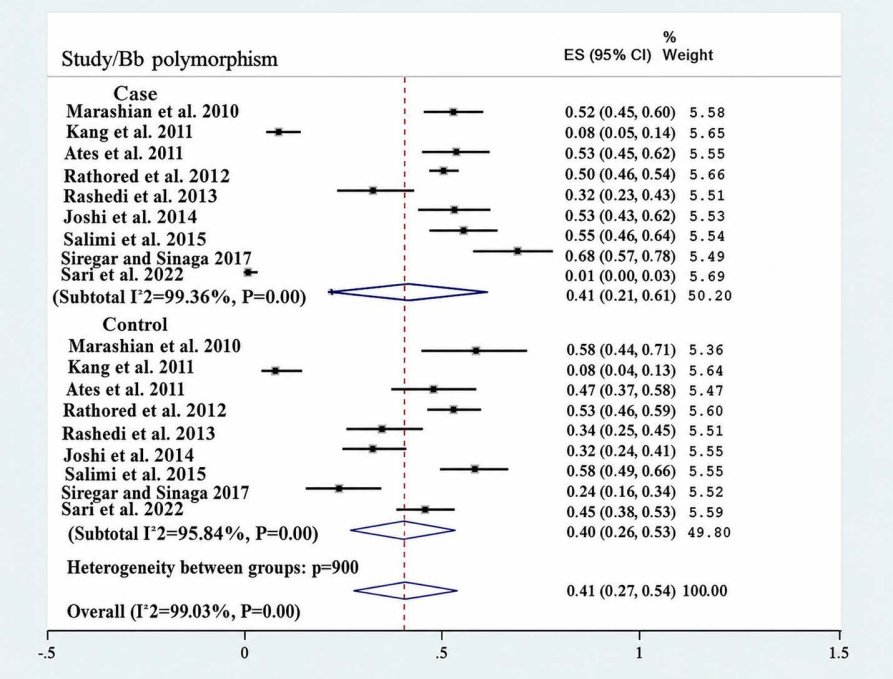

Figure 9. Studies evaluated based on the random effect model in the case and control groups (Study/Bb polymorphism). Effect size: ES

bb polymorphism was related to the study of Joshi et al. (India, 2014) (CI 95%: 0.85-0.96, ES = 0.92, weight: 5.94) (33) and the study of Salimi et al. (Iran, 2015) (CI 95%: 0.13-0.27, ES = 0.19, weight: 5.91) (27). In the control group, the highest prevalence rate associated with the polymorphism of this genotype was related to the research conducted by Siregar and Sinaga (Indonesia, 2017) (CI 95%: 0.63-0.82, ES = 0.74, weight: 5.84) (36). The lowest prevalence rate was also observed in the study conducted by Sari et al. (Indonesia, 2022) (CI 95%: 0.00-0.04, ES = 0.01, weight: 5.97) (22). The overall prevalence associated with the bb genotype polymorphism in the case group (95% CI: 0.23-0.66, ES = 0.45, weight: 47.19) was higher than in the control group (95% CI: 0.19-0.55, ES = 0.37, weight: 52.81) (Figure 10).

Total result

As a total result, the highest overall prevalence of VDR gene polymorphisms was found in genotypes; Aa (control) and bb (case) (each one ES = 0.45), AA (case, ES = 0.42), AA (control. ES = 0.32), Aa (control, ES = 0.42), Bb (case, ES = 0.41), Bb (control, ES = 0.40), bb (control, ES = 0.37), BB (case, ES = 0.26), BB (control ES = 0.25) and aa (control and case, ES = 0.22), respectively.

Discussion

Vitamin D exerts most of its physiological actions through VDR on target cells. VDR expression and function are thought to be influenced by VDR gene polymorphisms. Khan et al. in Saudi Arabia reported that the prevalence of VDR gene polymorphisms (using PCR-RFLP), including TaqI, ApaI, BsmI, and FokI, was found to be 70, 33, 50, and 25%, respectively (38). A study performed by Huang et al. in China showed that the prevalence of BsmI genotype polymorphisms (using a Multichannel fluorescence detector to identify SNPs) was 91.66 bb, 8.72 Bb, and 0.21% BB. The prevalence of allelic polymorphisms related to b and b was 95.43 and 4.57%, respectively (39). VDR mediates most genomic effects on target cells, such as lymphocytes. VDR changes may predispose individuals to certain diseases. Many studies have investigated the role of VDR gene polymorphisms in pulmonary TB, but the results are different. Rashedi et al. in Iran reported that the proportion of polymorphism (using PCR-RFLP) of the Aa genotype (53.3% versus 50%) was higher in healthy individuals than the patients (with pulmonary TB), but for the aa (15.47% versus 13.3%) and AA (34.52% versus 33.3%) genotypes, this rate was higher in patients compared to healthy individuals (3). Ismail et al. in Indonesia reported that VDR gene polymorphisms (using PCR-RFLP) were associated with the risk of developing pulmonary TB (40). The results of our study showed that the prevalence of VDR polymorphism was different and significant between cases (people with pulmonary TB with polymorphism of VDR genes) and controls (healthy people without pulmonary TB with polymorphism of VDR genes). The highest prevalence of polymorphisms of VDR-related genes in the case group was associated with the allele bb (45%); this rate in the control group was associated with Aa (45%). Rashedi et al. also reported that one-third of the world population is infected with TB, but only 10% of them have developed the disease. This refers to the difference in the activity of the host immune response against TB. Vitamin D and its receptor are important factors in the host immune response

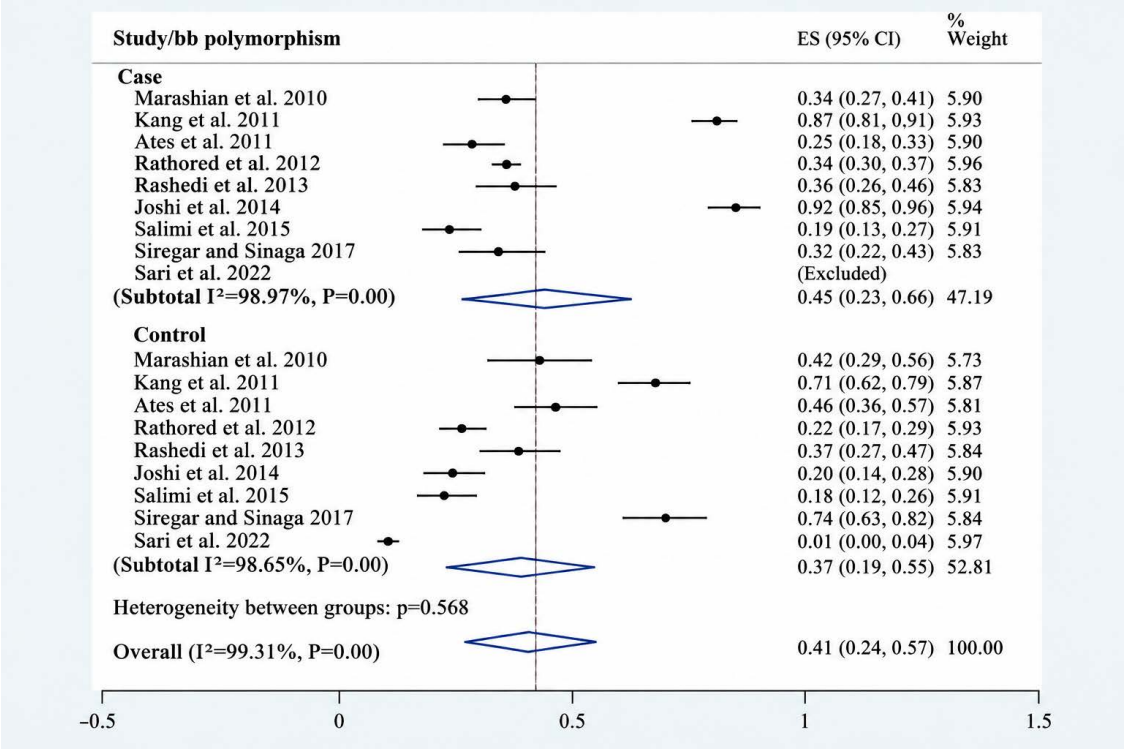

Figure 10. Studies evaluated based on the random effect model in the case and control groups (Study/bb polymorphism). Effect size: ES

against TB. In the study conducted by Rashedi et al, unlike our study, there was no statistically significant relationship between BsmI (BB, Bb, Bb) and ApaI (AA, Aa, aa) polymorphisms (PCR-RFLP) in the VDR gene and susceptibility to TB (patients with TB = 84 and healthy people = 90), but there was a significant correlation between the genotype prevalence of VDR gene polymorphisms with plasma vitamin D levels. Therefore, increasing the plasma level of vitamin D may protect them against active TB (3). In a similar study, Samimi et al, in a systematic review and meta-analysis in Iran, showed that VDR polymorphism has an effective role in susceptibility to pulmonary TB. It showed a significant association with susceptibility to pulmonary TB, which is consistent with the results of our study. In a study by Samimi et al, the prevalence of VDR polymorphisms in ApaI and BsmI was 39% and 37%, respectively (14). In our study, the prevalence of polymorphisms was different in the case and control groups. In the case of the ApaI gene, the prevalence of the AA genotype polymorphism was higher in the case group (ES = 0.42) compared to the control group (ES = 0.32). However, the prevalence of the aa genotype polymorphism was the same in the case and control groups (ES = 0.22). However, for the BsmI gene, the prevalence of polymorphisms in the case (BB = 0.26, Bb = 0.41, bb = 0.45) group was higher than the control group (BB = 0.25, Bb = 0.40, bb = 0.37). In the study by Shah et al. in India, 6320 patients with TB and 7047 controls were examined. These people with the BB genotype polymorphism (OR = 0.713) were less likely to be infected with TB. However, the aa genotype polymorphism had a significant role in the susceptibility to TB (OR = 1.997) (41). Mohammadi et al, in a systematic review and meta-analysis in Iran, reported that there was a significant and positive relationship between BsmI ((bb + bB/BB) and TB, but there were no significant relationships between ApaI TB (12). As the studies reported, among the results obtained, there is a fundamental lack of homogeneity worldwide, which makes it very difficult to draw absolute conclusions without considering other related genetic and environmental factors. Therefore, examining other genes, environmental factors, and their synergistic effects on a large population can help make a better and more complete judgment (3, 15). Yerezhepo et al. in Kazakhstan explained 411 people with pulmonary TB and 686 without a family history of pulmonary TB. Vitamin D deficiency was 95% in the case group and 43.7% in the control group. In our study, similar to the study of Yerezhepo et al, the highest rate of polymorphism (using Real-time PCR, allelic discrimination assay using TaqMan probes) was seen in the case group (42). In the studies conducted by Yu et al. in China (24) (using multiplex PCR- sequencing), Alexandra et al. in Romania (26) (using ARMS), and Siregar and Sinaga in Indonesia (using PCR-RFLP), the highest prevalence of AA (ES = 0.99), Aa (ES = 0.72), and aa (ES = 0.46) polymorphism was detected in the case group, respectively. The prevalence of the bb polymorphism (ES = 0.74) in the case group was higher than in the control group (36). Also, there was a significant association between VDR polymorphism and pulmonary TB in our results. The highest prevalence of BsmI polymorphism showed that the case group in all three genotypes BB (case; ES = 0.59), Bb (case; ES = 0.68), and bb (case; ES = 0.92) had the highest degree of polymorphism, which was present in the studies conducted by Sari et al. in Indonesia (using SNP genotyping- Real-Time PCR) (22), Siregar and Sinaga in Indonesia (36), and Joshi et al. in India (using PCR-RLFP) (33), respectively. Epidemiological data showed that social and economic factors, body mass index (BMI), workplace, and underlying diseases such as diabetes, sex, age, place of residence, smoking, and alcohol consumption are associated with a high risk of pulmonary TB. Therefore, the epidemiological and demographic characteristics of people in different nations, countries, and continents have been studied, and the demographic characteristics of the studied people show different results in different societies. On the other hand, there were different and variable numbers of case and control groups in different studies. Also, not all regions of a country are investigated, and the selection of case and control groups can be subject to potential biases. Serum vitamin D levels also depend on several factors, and potential biases must be considered. The mentioned causes us to observe different prevalence of polymorphisms in different communities and ethnic groups (36). However, the results obtained from Das and Chaubey's research in India were not consistent with those of our study, as no significant relationship was found between the incidence of TB and the prevalence of alleles or genotypes of ApaI and BsmI (using Next-generation sequencing) in global populations. However, they explained that the prevalence of ApaI and BsmI genotypes behaved differently in South Asian populations compared to West and East Eurasian populations. According to Das and Chaubey's results, ancestral ApaI and BsmI alleles exist with more than 50% prevalence in modern human populations. These SNPs also have very strong linkage disequilibrium between all population groups, and based on ethnic and racial differences, there can be a significant or insignificant relationship between the incidence of TB and the prevalence of the ApaI and BsmI allele or genotype (43). In a study conducted by Varahram et al. in Iran, the prevalence of BsmI polymorphism (using PCR-RFLP) was significantly higher in patients with pulmonary TB than in healthy individuals. Consistent with our review, Varahram et al. also confirmed the association of BsmI polymorphism with susceptibility to pulmonary TB. Therefore, host genetic susceptibility to TB can be determined through case-control studies and comparison of genotypes between groups. Differences in the polymorphism of these genes to susceptibility to TB can be used to assess the risk of TB in the world population (44). PCR-RFLP analysis in families can then show who is at risk for the disease or who is likely to be a carrier of the mutated gene. PCR-RFLP testing is also used to identify and differentiate organisms by analyzing unique patterns in the genome. It is also used to identify the extent of recombination at sites between

restriction fragments (45). By examining the genotype of patients who have severe TB and are disabled, more useful methods with higher efficiency can be used to control and treat these patients (46).

The present study was conducted as a meta-analysis and meta-analysis study on the global population with a large number of samples, so the results obtained can be more accurate and can be generalized to other studies. Also, the analysis was evaluated as case-control, which provides the possibility of comparing two groups. The difference in the amount of polymorphism of these genes concerning susceptibility to TB can be used to assess the risk of TB in different healthy and diseased populations. The present review is limited to a certain time range, and it is better to consider a longer time range in future studies. Also, due to the large volume of results and tables, not all the variables have been analyzed. In this case, it is suggested that separate articles be analyzed along with the analysis of variables affecting polymorphism, such as underlying and genetic diseases, and different regions of the world be compared and analyzed with each other. To access the full text of a number of articles, it was necessary to pay a fee, considering that the payment from Iran in dollars was expensive, and the payment methods were also sanctioned. Some articles did not mention some variables surveyed in this article.

Conclusion

There was a significant difference in the prevalence of polymorphism between the two groups of cases and controls. The highest prevalence of polymorphisms in the case group was associated with the alleles: bb, AA, Aa, Bb, BB, and aa, respectively. In the control group, the highest prevalence of polymorphisms was shown in the alleles Aa, Bb, bb, AA, BB, and aa, respectively.

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Authors' Contribution

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Visualization: Hossein Ghorbani.
Writing–Original Draft: Sara Ghofrani Tabari, Samaneh Rouhi.

Data Availability Statement

All necessary data will be available from the corresponding author upon reasonable request.

Ethical Approval

This research was approved under the supervision of the Medical Ethics Committee of Babol University of Medical Sciences (Ethical code: IR.MUBABOL.REC.1402.004).

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