Association between thrombophilic gene variants and thrombosis in the Iranian population: a systematic review and meta-analysis

Seyed Mehrab Safdari[a], Azadeh Rezazadeh[b], Danial Habibi[c], Samin Alavi[d], Mahmood Shams[e], Ali Noroozi-Aghideh[f] and Akbar Dorgalaleh[g]

Thrombophilia is influenced by genetic variants, such as Factor V Leiden (FVL) and the prothrombin G20210A mutation. In clinical settings, assessing numerous genetic factors can lead to diagnostic errors and unnecessary treatments. This meta-analysis examines gene variants associated with thrombosis in the Iranian population, where their role in thrombotic disorders remains underexplored. A systematic literature search was performed across PubMed, Scopus, and Web of Science, targeting case-control studies published up to July 2025. Studies were included if they evaluated thrombophilia-related polymorphisms in Iranian patients with various thrombotic conditions, such as recurrent pregnancy loss (RPL), venous thromboembolism (VTE), or deep vein thrombosis (DVT). Advanced statistical analyses, including random-effects models, fixed-effects models, and Bayesian meta-analysis, were used to compute odds ratios (ORs) and 95% confidence intervals (CIs). From 36 studies encompassing over 14 000 participants, significant associations emerged. For RPL, FVL G1691A heterozygote (OR: 1.998, 95% CI: 1.02–3.88), methylenetetrahydrofolate reductase (MTHFR) C677T heterozygote (OR: 1.77, 95% CI: 1.31–2.39), MTHFR A1298C heterozygote (OR: 3.10, 95% CI: 1.33–7.20) and homozygote (OR: 1.69, 95% CI: 1.05–2.70), prothrombin G20210A heterozygote (OR: 2.435, 95% CI: 1.09–5.39) and homozygote (OR: 0.487, 95% CI: 0.40–0.58), plasminogen activator inhibitor-1 (PAI-1) polymorphisms, factor V (FV) A4070G, FV 5279A/G, factor XIII (FXIII) Val34Leu, and integrin subunit beta-3 (ITGB3)1565T/C were linked to elevated RPL risk. Additionally, FVL G1691A heterozygote (OR: 5.25, 95% CI: 2.39–11.54) was associated with higher VTE risk, while MTHFR C677T heterozygote (OR: 1.404, 95% CI: 1.030–1.914) increased DVT risk. These ethnicity-specific findings highlight critical genetic risk factors for thrombotic disorders in Iranians, potentially guiding precise diagnostics and personalized interventions. *Blood Coagul Fibrinolysis* **36:349–363**

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[a]Department of Hematology and Blood Transfusion, School of Allied Medicine, Iran University of Medical Sciences, [b]Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, [c]Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, [d]Pediatric Congenital Hematologic Disorders Research Center, Research Institute for Children's Health, Shahid Beheshti University of Medical Sciences, Tehran, [e]Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, [f]Department of Hematology, School of Allied Medical Sciences, AJA University of Medical Sciences and [g]Hamin Pazhuhan Tis Institute, Tehran, Iran

Correspondence to Akbar Dorgalaleh, Hamin Pazhuhan Tis Institute, Tehran 148 775 5693, Iran.
E-mail: dorgalaleha@gmail.com

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Introduction

Thrombophilia encompasses a spectrum of disorders characterized by an increased tendency for thrombus formation, thereby predisposing individuals to venous or arterial thromboembolic events. These thrombotic conditions represent a significant contributor to global morbidity and mortality. The etiology of thrombophilia may be classified into inherited or acquired forms, with approximately 40% of cases attributed to genetic predispositions [1,2].

Inherited thrombophilia plays a significant role in the pathogenesis of thrombotic disorders, as supported by substantial evidence. Numerous genetic polymorphisms associated with thrombophilia have been identified, which contribute to an increased risk of thromboembolic conditions, including deep vein thrombosis (DVT), pulmonary embolism (PE), and recurrent pregnancy loss (RPL). Understanding and recognizing genetic predispositions are critical for accurate diagnosis, effective prevention, and optimal management of various health conditions. Genetic factors play a significant role in the development of many diseases, influencing an individual's susceptibility, the course of the disease, and their response to treatments. Advancements in genomic technologies have transformed the ability to detect hereditary patterns and genetic variants, enhancing healthcare providers capacity to evaluate patient risk more precisely. These developments facilitate personalized treatments and targeted interventions that meet individual needs. The identification of genetic predispositions enables the implementation of preventive strategies, including lifestyle modifications, proactive medical interventions, and routine monitoring for individuals at elevated risk. Advanced methodologies such as next-generation sequencing (NGS) and polygenic risk scoring play a pivotal

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role in the precise detection of these genetic factors. These innovative approaches facilitate the development of more personalized and effective healthcare strategies, thereby advancing the field of precision medicine [3].

Factor V Leiden (FVL G1691A) and prothrombin gene mutation (G20210A) are the most common genetic contributors to thrombophilia, together accounting for roughly 50% to 70% of identified cases of inherited thrombophilia [4]. Additional genetic risk factors have been identified, including mutations in genes encoding coagulation factors (Factor V, Factor XIII, and fibrinogen β), abnormalities in the fibrinolytic system (PAI-1), elevated levels of homocysteine (MTHFR), and variations in the angiotensin-converting enzyme (ACE). Mutations in these genes significantly elevate the risk of developing thromboembolism [5].

Genetic predispositions, particularly thrombophilia-associated polymorphisms, play a critical role in the pathogenesis of thrombotic disorders. Although these genetic factors have been extensively studied on a global scale, there remains a paucity of research addressing their prevalence and impact within the Iranian population. This gap is significant given the potential for ethnic-specific genetic variations to influence susceptibility to thrombotic conditions.

This systematic review and meta-analysis aim to evaluate the association between thrombophilia-related genetic variants and thrombotic disorders within the Iranian population. The study focuses on key polymorphisms implicated in thrombosis, analyzing their contribution to disease susceptibility and progression. By clarifying the impact of these mutations, this study aims to enhance diagnostic precision, inform targeted treatments, and propose cost-effective prevention strategies, thereby reducing the burden of thrombotic diseases among Iranian patients.

Materials and methods

This systematic review and meta-analysis adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [6], ensuring a standardized and transparent process for study selection and synthesis. A comprehensive search was conducted across multiple databases using predefined inclusion and exclusion criteria to minimize bias. Two independent reviewers extracted the data, resolving disagreements through discussion or consultation with a third reviewer. Study quality was assessed with validated tools, and statistical analyses, including heterogeneity assessment, were performed using meta-analytic techniques. This rigorous methodology aims to provide robust evidence to inform clinical decisions and guide future research.

A comprehensive literature search identified 301 articles relevant to our study objectives. Following the removal of 76 duplicate entries, 225 articles underwent title and abstract screening. Of these, 108 were excluded due to irrelevance to the research question. Further full-text evaluation led to the exclusion of an additional 65 articles for the following reasons: Review studies ($n = 8$), case reports ($n = 5$), lack of statistical analysis ($n = 20$), insufficient data for outcome assessment, specifically missing odds ratios (ORs) ($n = 25$), duplication of study population and results ($n = 3$), and inability to access full text ($n = 4$). After rigorous screening and application of inclusion criteria, a final set of 52 articles was deemed eligible for qualitative analysis, and 36 articles were eligible for quantitative analysis or meta-analysis. These studies represent a robust foundation for addressing the research objectives. A detailed flow diagram outlining the search strategy and study selection process is provided in Figure 1. This systematic approach ensures methodological rigor and enhances the reliability of the findings derived from the selected literature.

Study selection

A comprehensive search of published studies was conducted across multiple databases, including PubMed, SCOPUS, Web of Science, SID, and Magiran (Iran's Publications Database), covering the data period from January 1, 2003, to July 1, 2025. The search was restricted to articles published in English or Persian and focused exclusively on studies involving human subjects. All relevant publications were identified using predefined keywords without imposing additional restrictions. Titles and abstracts of the retrieved records were thoroughly screened for relevance. To enhance the comprehensiveness of the search, reference lists of the included articles were reviewed for additional original studies. Furthermore, a supplementary search was performed using Google Scholar to ensure no pertinent articles were overlooked. Studies that passed the initial screening underwent a full-text review conducted independently by an investigator. Detailed information regarding the search strategy and protocol is provided in the Data Supplementary file, http://links.lww.com/BCF/A191.

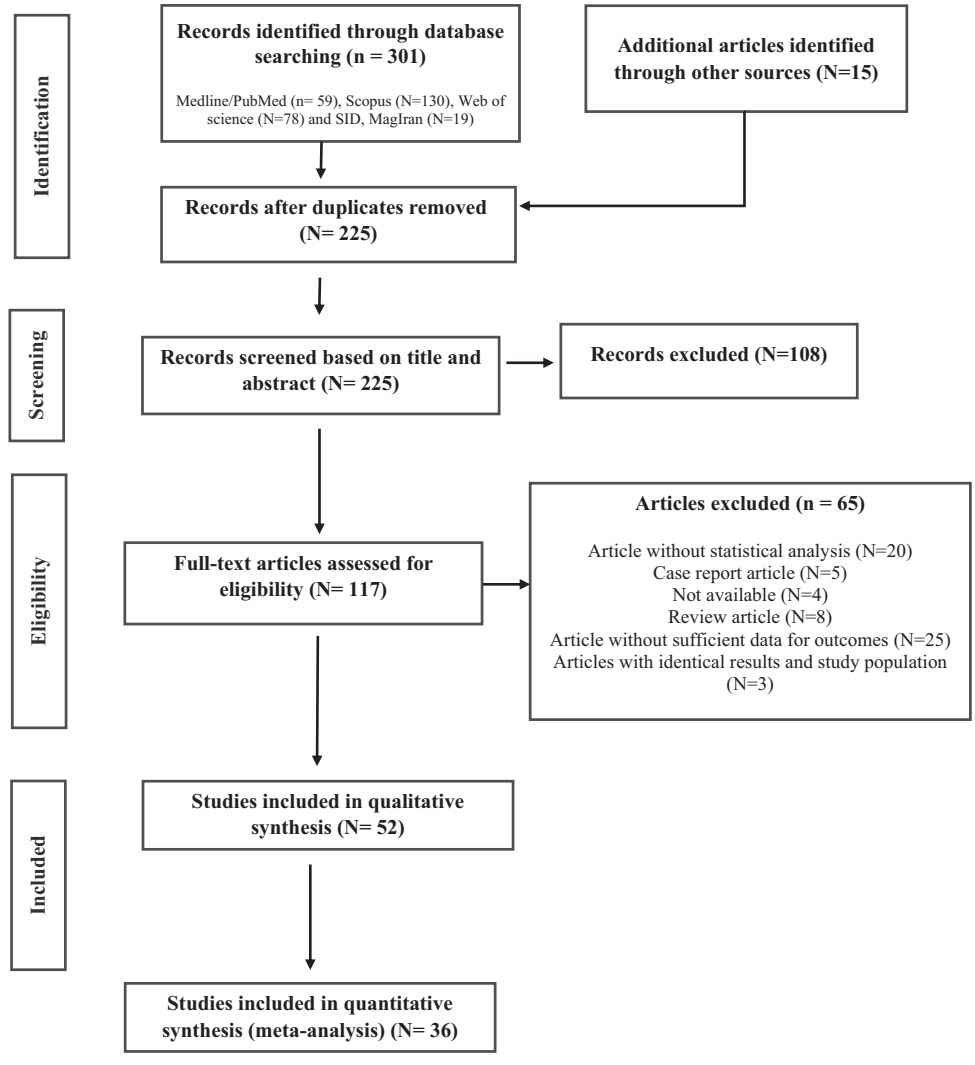
The criteria for inclusion required the following: studies with a case-control design, availability as full-text articles, research conducted on Iranian populations, investigations examining the relationship between thrombophilia gene polymorphisms and thrombotic disorders, sufficient data provided to calculate ORs with 95% confidence intervals (CIs), including the number of cases, controls, and events in each group, and publications in English or Persian.

The criteria for excluding studies were as follows: abstracts, case reports, editorials, and review articles, studies lacking a control group, research involving animals, studies where the outcome could not be determined, and duplicate datasets derived from the same study.

Data extraction

The studies were independently assessed for eligibility by two reviewers. Any discrepancies were addressed and

Fig. 1



The search strategy based on PRISMA protocol.

resolved through consultation with the study supervisor (A–D) when necessary. Utilizing the established inclusion and exclusion criteria, the following data were systematically extracted from each study: the first author's last name, publication date, country of origin, clinical presentation of thrombosis, genetic polymorphisms, total cases and controls, number of events observed in both patients and controls, prevalence rates in each group, ORs, and corresponding confidence intervals.

Statistical analysis

The main quantitative analysis focused on the risk of all thrombotic disorders associated with each type of thrombophilia gene polymorphism. Random and Fixed effects models were applied in the current meta-analysis. The risks were measured using OR with their 95% CIs. Data analysis was performed using *Stata* software, version 14.0 (Stata Corp LP, College Station, TX, USA). A *P*-value of 0.05 was considered statistically significant.

Due to the limited number of studies, we also employed a Bayesian approach for binary outcomes using the Bayesmeta package in *R4.2.2* software. Effect sizes and standard errors were calculated using the escalc function in the metafor package. For the random-effects meta-analysis, we specified priors for the unknown parameters μ and σ. A half-normal prior with a scale of 0.5 was used for heterogeneity, with $\mu = 0$ (corresponding to an OR of 1) and $\sigma = 4$ (corresponding to the unit information prior).

The meta-analysis examined the association between various genetic polymorphisms and their potential link to conditions such as cerebral venous sinus thrombosis (CVST), DVT, RPL, preeclampsia, and venous thromboembolism (VTE).

For the association between CVST and FVL G1691A polymorphism, the heterozygote model (GA) was predominantly used due to its established association with an increased risk of thrombosis. The MTHFR C677T polymorphism was analyzed under both homozygote (TT) and heterozygote (CT) models to evaluate the impact of different genotypic combinations in CVST. For DVT, the heterozygote models (GA, CT, and AC) were applied to FVL G1691A, MTHFR C677T, and MTHFR A1298C polymorphisms, respectively, as these genotypes are commonly observed in DVT cases. In RPL, both homozygote and heterozygote models were utilized to assess the potential effects of all polymorphisms comprehensively. In the context of preeclampsia and VTE, the FVL G1691A polymorphism was analyzed under the heterozygote model (GA) based on its relevance in existing studies.

To assess the presence and degree of heterogeneity among the included studies, both a *Q*-test based on the chi-square distribution and I^2 statistics were utilized. The *Q*-test was employed to determine statistical significance, with a *P*-value of <0.05 indicating significant heterogeneity. Conversely, a *Q*-test *P*-value >0.05 suggested the absence of statistically significant heterogeneity among the analyzed studies. The I^2 statistic quantifies the proportion of total variation across studies that is attributable to heterogeneity rather than chance. An I^2 value of 0% indicates no observed heterogeneity, whereas values of 25%, 50%, and 75% correspond to low, moderate, and high levels of heterogeneity, respectively. Values exceeding 75% were categorized as extreme heterogeneity.

Results

Characteristics of included studies

A comprehensive search strategy and manual retrieval identified a total of 301 articles relevant to our study. Following the removal of duplicate publications, 76 articles were excluded. An additional 108 articles were excluded after a preliminary screening of titles and abstracts, and a further 65 articles were deemed unsuitable following a full-text review. Consequently, 52 articles were retained for qualitative synthesis, while 36 articles were included in quantitative synthesis (meta-analysis). The body of literature reviewed spans publications from 2003 to 2025, encompassing over 14 000 cases and controls. Notably, all observational studies included in this analysis were case-control studies. These studies were exclusively conducted in Iran, providing a focused geographical context for our findings. This systematic approach ensures a robust foundation for both qualitative and quantitative analyses, contributing valuable insights into the field.

As presented in Tables 1–5, a total of 36 case-series studies were incorporated into the final quantitative synthesis (meta-analysis). The distribution of specific genotypes among patients (cases) and healthy individuals (controls) for each clinical condition is summarized in Table 6.

In CVST, six cases and three controls were heterozygous for the FVL G1691A mutation, 57 cases and 89 controls were heterozygous for the MTHFR C677T mutation, and 39 cases and 65 controls were homozygous for MTHFR C677T. For VTE, 31 cases and 13 controls were FVL G1691A heterozygotes, while 105 cases and 177 controls were MTHFR C677T heterozygotes. In DVT, 172 cases and 249 controls were homozygous for MTHFR C677T, and 145 cases and 87 controls were heterozygous for MTHFR A1298C. In RPL, heterozygosity for FVL G1691A was observed in 157 cases and 42 controls, and homozygosity in 204 cases and 160 controls. Prothrombin G20210A heterozygosity was found in 87 cases and 20 controls. For the MTHFR C677T gene, 449 cases and 246 controls were heterozygous, and 47 cases and 34 controls were homozygous, while 478 cases and 178 controls were heterozygous and 74 cases and 32 controls were homozygous for the MTHFR A1298C variant. Combined MTHFR C677T and A1298C mutations were present in 41 cases and 10 controls. Heterozygosity for Factor V A5279G and A4070G was seen in 107 and 23 cases, and 20 and 15 controls, respectively. For β-fibrinogen (-455G/A) and ACE (intron 16I/D), heterozygosity was observed in 251 cases and 148 controls, respectively, for β-fibrinogen (- 455G/A), and in 139 cases and 113 controls, respectively, for ACE (intron 16I/D). Carriers of the integrin subunit beta-3 (ITGB3)1565T/C variant included 57 cases and 134 controls. The PAI-1 (−675I/D, 5G/4G) polymorphism was identified in 518 cases and 226 controls, with the homozygous 4G/4G genotype present in 202 cases and 24 controls. Additionally, 421 cases and 432 controls were homozygous for the Prothrombin G20210A variant, and 127 cases and 81 controls carried the FXIII Val34Leu variant. In preeclampsia, 32 cases and 10 controls were carriers of the FVL G1691A mutation.

Quality assessment

The quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) by two independent authors, based on eight key criteria: proper identification of the cases, representativeness of the cases, selection and definition of controls, comparability between cases and controls, assessment of exposure, use of the same method to assess exposure in both groups, and nonresponse rate. The maximum possible score was 9, with higher scores indicating better quality. Studies scoring below 5 were excluded from the analysis (see Data Supplementary, http://links.lww.com/BCF/A191).

Quantitative synthesis

Cerebral venous sinus thrombosis

Three studies investigated the relationship between thrombophilia gene polymorphisms and CVST, considering both

heterozygous and homozygous genotypes [7–9]. The details of the studies are presented in Table 1.

The relation between heterozygosity for the Factor V Leiden G1691A mutation and cerebral venous sinus thrombosis

Two studies evaluated the association between FVL G1691A heterozygosity and CVST [7,8]. The findings indicated that the FVL G1691A heterozygous state does not significantly raise CVST risk, with an OR of 1.82 (95% CI: 0.07–43.93) and significant heterogeneity ($I^2 = 88.2\%$, $P = 0.004$). Additionally, the corresponding log OR (95% credible interval) was 1.74 (0.17–3.29) for FVL G1691A heterozygotes.

The relation between heterozygosity for the MTHFR C677T mutation and cerebral venous sinus thrombosis

The association between MTHFR C677T heterozygosity and CVST was assessed in three studies [7–9], which showed no significant increased risk (OR: 1.03, 95% CI: 0.45–2.33) with moderate but non-significant heterogeneity ($I^2 = 65.3\%$, $P = 0.056$). The corresponding log OR (95% credible interval) was 0.52 (−0.12–1.16) for MTHFR C677T heterozygotes.

The relation between homozygosity for the MTHFR C677T mutation and cerebral venous sinus thrombosis

Based on the findings from the three abovementioned studies, there was no significant association between homozygosity for the MTHFR C677T mutation and the increased risk of CVST [7–9]. The OR was calculated as 1.031 (95% CI: 0.36–2.9), indicating no significant correlation. Additionally, heterogeneity was not statistically significant ($I^2 = 63.7\%$, $P = 0.064$). Furthermore, the log OR for MTHFR C677T homozygotes, along with its credible interval, was reported as 0.65 (−0.09–1.39), reinforcing the lack of a significant association.

Deep vein thrombosis

Several studies within Iranian literature have explored the relationship between polymorphisms in thrombophilia genes and the risk of developing DVT. These investigations have examined the genetic variations in both heterozygous and homozygous states [10–13]. The details of these studies are presented in Table 2.

The relation between heterozygosity for the Factor V Leiden G1691A mutation and deep vein thrombosis

The association between DVT and heterozygosity for the FVL G1691A mutation has been demonstrated in three case-control studies [10–12]. These studies indicated an overall fivefold increased risk, with an OR of 5.25 (95% CI: 2.39–11.54). Notably, there was no evidence of statistical heterogeneity among the studies ($I^2 = 0\%$, $P = 0.612$). Additionally, the corresponding log OR was reported as 1.95, with a 95% credible interval ranging from 0.92 to 3.

The relation between homozygosity for the MTHFR C677T and deep vein thrombosis

The effect of homozygote mutation for MTHFR C677T on DVT has been evaluated [10–13]. The findings indicated significant heterogeneity ($I^2 = 75\%$, $P = 0.007$) in the analysis. It was determined that the MTHFR C677T homozygous polymorphism does not contribute to an increased risk of DVT, as evidenced by an OR of 1.73 (95% CI: 0.88–3.4). Additionally, the corresponding log OR calculated using 95% credible intervals was 0.45, with a range of −0.28 to 1.24, further supporting the conclusion.

The relation between heterozygosity for the MTHFR A1298C mutation and deep vein thrombosis

An analysis of two studies investigating the association between the MTHFR A1298C heterozygous mutation and DVT indicated that this polymorphism does not significantly increase the risk of DVT. The pooled OR was estimated at 3.1 (95% CI: 0.33–28.69), indicating no statistically significant association. Furthermore, there was considerable heterogeneity between the studies ($I^2 = 81.7\%$, $P = 0.019$), suggesting substantial variability in the results. A Bayesian analysis yielded a log OR of 1.01 with 95% credible intervals ranging from -0.29 to 2.30, further supporting the conclusion that the MTHFR A1298C polymorphism has no meaningful effect on the risk of developing DVT [11,13].

Table 1 Characteristics of studies including FVL G1691A and, MTHFR C677T polymorphisms and CVST

First author (Ref)	Year	Number of cases	Number of controls	Genotypes		Number of events in patients (%)		Number of events in controls (%)		Lower Limit		Upper Limit		OR	
				Hetero	Homo	Hetero	Homo	Hetero	Homo	Hetero	Homo	Hetero	Homo	Hetero	Homo
FVL G1691A															
Rahimi *et al.* [7]	2010	24	100	Heterozygote		4 (16.7)		2 (2)		1.68		57.2		9.8	
Saadatnia *et al.* [8]	2015	40	51	Heterozygote		2 (5)		1 (2.5)		0.33		4.384		0.38	
MTHFR C677T															
Rahimi *et al.* [7]	2010	24	100	Hetero	Homo	14 (58.3)	14 (58.3)	44	44	0.73	0.73	4.5	4.5	1.82	1.82
Saadatnia *et al.* [8]	2015	40	51	Hetero	Homo	22 (56.3)	22 (56.3)	43.8	50	0.191	0.191	1.041	1.041	0.446	0.446
Ghaznavi *et al.* [9]	2015	50	50	Hetero	Homo	21 (42)	3 (6)	27 (36)	3 (6)	0.64	0.32	2.84	9.21	1.35	1.73

CSVT, cerebral sinus venous thrombosis; FVL, Factor V Leiden; Hetero, heterozygote; Homo, homozygote; MTHFR, methylenetetrahydrofolatereductase; OR, odds ratio.

Table 2 Characteristics of studies including FVL G1691A, MTHFR C677T and, MTHFR A1298C polymorphisms and DVT

First author (Ref)	Year	Number of cases	Number of controls	Genotypes	Number of events in patients (%)	Number of events in controls (%)	Lower limit	Upper limit	OR
FVL G1691A									
Rahimi *et al.* [10]	2010	80	100	Heterozygote	7 (11.4)	2 (2)	1.32	30.05	6.3
Hosseini *et al.* [11]	2015	182	250	Heterozygote	18 (9.9)	4 (1.6)	2.2	20.03	6.7
Karimi *et al.* [12]	2015	35	306	Heterozygote	2 (5.7)	0 (0)	0.52	12.98	2.59
MTHFR C677T									
Rahimi *et al.* [10]	2010	80	100	Homozygote	49 (38.7)	56 (44)	0.44	1.46	0.8
Hosseini *et al.* [11]	2015	182	250	Homozygote	20 (10.9)	5 (2)	2.2	16.4	6
Karimi *et al.* [12]	2015	35	306	Homozygote	18 (51.4)	0 (0)	0.93	3.81	1.89
Ghaffari *et al.* [13]	2014	120	100	Homozygote	85 (70.8)	78 (78)	0.83	2.31	1.43
MTHFR A1298C									
Hosseini *et al.* [11]	2015	182	250	Heterozygote	57 (31.3)	13 (5.2)	4.4	15.8	8.3
Ghaffari *et al.* [13]	2014	120	100	Heterozygote	88 (73.3)	74 (74)	0.14	5.32	0.83

DVT, deep venous thrombosis; FVL, Factor V Leiden; MTHFR, methylenetetrahydrofolate reductase; OR, odds ratio.

Recurrent pregnancy loss

RPL has been extensively studied among thrombotic disorders, with various definitions such as two or more pregnancy losses, three or more pregnancy losses, recurrent abortion, and spontaneous abortion being collectively categorized as RPL in research contexts. This meta-analysis comprehensively evaluated 23 studies to investigate the association between thrombophilia gene polymorphisms and RPL. Both heterozygote and homozygote genetic models were examined to identify potential genetic factors contributing to RPL [14–36]. The details of these studies are presented in Table 3.

The relation between heterozygosity for the Factor V Leiden G1691A mutation and recurrent pregnancy loss

Nine studies assessed the association between the FVL G1691A heterozygous mutation and RPL [14–22]. The pooled analysis indicated that the FVL G1691A heterozygous polymorphism was associated with an increased risk of RPL (OR: 1.998; 95% CI: 1.02–3.88). However, substantial heterogeneity was observed ($I^2 = 82.7\%$, $P < 0.001$). Furthermore, the corresponding log OR based on the Bayesian analysis was 1.13 with a 95% credible interval of 0.60–1.65, suggesting no statistically significant association.

The relation between homozygosity for the Factor V Leiden G1691A mutation and recurrent pregnancy loss

The association between the FVL G1691A homozygous mutation and RPL was evaluated in two studies [19,20]. The analysis indicated that there was no increased risk of RPL associated with the FVL G1691A homozygote polymorphism (OR: 0.356, 95% CI: 0.10–1.23), and no heterogeneity was observed ($I^2 = 0\%$, $P = 0.742$). The corresponding log OR for FVL G1691A homozygote with 95% credible intervals was found to be −0.97 (−2.33–0.40).

The relation between heterozygosity for the MTHFR C677T mutation and recurrent pregnancy loss

Eight studies investigated the potential association between the MTHFR C677T heterozygous mutation and the risk of RPL [14,16,18,22–26]. The results revealed that the heterozygous MTHFR C677T polymorphism increased the risk of RPL (OR: 1.77, 95% CI: 1.31–2.39), with heterogeneity ($I^2 = 54.8\%$, $P = 0.030$). The corresponding log OR for the MTHFR C677T heterozygote with 95% credible intervals was 0.73 (0.32–1.21).

The relation between homozygosity for the MTHFR C677T mutation and recurrent pregnancy loss

Four studies assessed the correlation between the MTHFR C677T homozygote mutation and RPL [20,24–26]. Results demonstrated that there was no increased risk of RPL due to the homozygote MTHFR C677T polymorphism (OR: 1.058, 95% CI: 0.657–1.70), and there was no significant heterogeneity ($I^2 = 2.4\%$, $P = 0.380$). The corresponding log OR for the MTHFR C677T homozygote was found to be 0.06 (95% credible interval: -0.55–0.69).

The relation between heterozygosity for the MTHFR A1298C mutation and recurrent pregnancy loss

The association between the MTHFR A1298C heterozygous mutation and RPL has been reported in nine studies [14,16,18,21–26]. Data on the association between the MTHFR A1298C heterozygous mutation and RPL demonstrated an overall threefold increased risk (OR: 3.10; 95% CI: 1.33–7.20). However, significant heterogeneity was observed among the included studies ($I^2 = 92.7\%$, $P < 0.001$). In contrast, the corresponding log OR based on the Bayesian analysis was 1.17, with a 95% credible interval of 0.61–1.72, suggesting no statistically significant association.

The relation between homozygosity for the MTHFR A1298C mutation and recurrent pregnancy loss

The relationship between the MTHFR A1298C homozygous mutation and the risk of RPL was examined in four studies [20,24–26]. Based on the results, individuals with the MTHFR A1298C homozygous polymorphism had an increased risk of RPL (OR: 1.69; 95% CI: 1.05–2.70). No considerable heterogeneity was detected

among the included studies ($I^2 = 49.3\%$, $P = 0.116$). However, the corresponding log OR based on the Bayesian analysis was 0.59, with a 95% credible interval of −0.05 to 1.27, suggesting that the association may not be statistically significant when evaluated using Bayesian methods.

The relation between the combination of heterozygosity for the MTHFR C677T and MTHFR A1298C mutations and recurrent pregnancy loss

Two studies assessed the correlation between a combination of heterozygosity for MTHFR C677T and MTHFR A1298C mutations and RPL [14,25]. The results revealed significant heterogeneity ($I^2 = 86.8\%$, $P = 0.006$) and indicated no correlation between these two combinations and the risk of RPL (OR: 3.85, 95% CI: 0.43–34.28). The corresponding log OR for the MTHFR C677T and A1298C combination was found to be 1.43 (0.25–2.62) with 95% credible intervals.

The relation between heterozygosity for the prothrombin G20210A mutation and recurrent pregnancy loss

The association between the prothrombin G20210A heterozygous mutation and RPL was assessed in seven studies [14,16,17,19,22,27,28]. The results demonstrated moderate heterogeneity among the included studies ($I^2 = 66.4\%$, $P = 0.007$) and showed a significant association between the prothrombin G20210A heterozygous polymorphism and an increased risk of RPL (OR: 2.44; 95% CI: 1.09–5.39). However, the corresponding log OR based on the Bayesian analysis was 1.04, with a 95% credible interval of 0.31–1.84, suggesting that the association was not statistically significant when evaluated using Bayesian methods.

The relation between homozygosity for the prothrombin G20210A homozygote mutation and recurrent pregnancy loss

Three studies assessed the association between homozygosity for the prothrombin G20210A mutation and RPL, and the analysis suggested a potential correlation (OR: 0.487, 95% CI: 0.40–0.58) [27–29]. No significant heterogeneity was observed across the included studies ($I^2 = 65.3\%$, $P = 0.056$). The corresponding log OR for the prothrombin G20210A homozygosity was −1.11, with a 95% credible interval of -2.23 to 0, suggesting no statistically significant association between the homozygous mutation and the risk of RPL based on the Bayesian analysis.

The relation between PAI-1 (−675 I/D, 5G/4G) mutation and recurrent pregnancy loss

Seven studies evaluated the association between the PAI-1 (−675 I/D, 5G/4G) polymorphism and the risk of RPL [17,18,22,23,29–31]. Our analysis revealed considerable heterogeneity among the included studies ($I^2 = 85.2\%$, $P < 0.001$). Despite the heterogeneity, a significant association was observed between the PAI-1 (−675 I/D, 5G/4G) polymorphism and an increased risk of RPL, with a pooled OR of 2.13 (95% CI: 1.18–3.85). However, the corresponding Bayesian log OR with 95% credible intervals was reported as 0.6 (0–1.18), which does not support a significant association. These conflicting results between the frequentist and Bayesian analyses suggest that the association between PAI-1 (−675 I/D, 5G/4G) and RPL remains uncertain and may be influenced by the considerable heterogeneity observed across studies.

The relation between homozygosity for the PAI-1 mutation and recurrent pregnancy loss

Five studies assessed the association between PAI-1 homozygous (4G/4G) polymorphism and the risk of RPL [29–33]. The meta-analysis revealed a significant association, with individuals carrying the homozygous 4G/4G genotype having an increased risk of RPL (OR = 7.08, 95% CI: 4.09–12.27). Moderate heterogeneity was observed across the included studies, though it was not statistically significant ($I^2 = 53.1\%$, $P = 0.058$). Additionally, the corresponding Bayesian log OR was 1.73, with 95% credible intervals of 0.98 to 2.57, suggesting a potential but not definitive association under the Bayesian framework. These findings indicate a strong association between the PAI-1 homozygous (4G/4G) polymorphism and RPL, based on frequentist analysis. However, the Bayesian results suggest a more cautious interpretation, highlighting some uncertainty regarding the strength of the association.

The relation between heterozygosity for the Factor V A4070G mutation and recurrent pregnancy loss

The association between Factor V A4070G heterozygosity and the risk of RPL was investigated in three studies [17,22,34]. The meta-analysis showed no heterogeneity among these studies ($I^2 = 0\%$, $P = 0.491$). The pooled analysis indicated a significant association between Factor V A4070G heterozygous mutation and an increased risk of RPL, with an OR of 2.26 (95% CI: 1.09–4.68). However, the corresponding Bayesian log OR was 0.29, with 95% credible intervals ranging from −0.71 to 1.28, suggesting no significant association under the Bayesian framework.

The relation between heterozygosity for the β-fibrinogen mutation and recurrent pregnancy loss

Seven studies examined the association between the β-fibrinogen (−455G/A) heterozygous mutation and the risk of RPL [17,18,21–23,35,36].. The results revealed significant heterogeneity among the studies ($I^2 = 82.6\%$, $P < 0.001$). The pooled analysis did not reveal a statistically significant association between the β-fibrinogen (−455G/A) heterozygous mutation and the risk of RPL (OR = 1.51, 95% CI: 0.74–3.10). Similarly, the Bayesian analysis produced a corresponding log OR of 0.42, with

95% credible intervals ranging from -0.20 to 1.03, indicating no significant association.

The relation between heterozygosity for the angiotensin-converting enzyme mutation and recurrent pregnancy loss

Three studies assessed the association between the ACE (intron 16 I/D) heterozygous polymorphism and the risk of RPL [17,30,35]. The meta-analysis revealed considerable heterogeneity among the included studies ($I^2 = 72.7\%$, $P = 0.026$). The pooled results showed no significant association between the ACE (intron 16 I/D) heterozygous polymorphism and the risk of RPL, with an OR of 1.48 (95% CI: 0.99–2.20). The corresponding Bayesian OR, expressed on the log-odds scale, was −0.23 with 95% credible intervals ranging from −1.11 to 0.56, indicating no significant association.

The relation between homozygosity for the ITGB3 1565T/C mutation and recurrent pregnancy loss

Out of three studies that assessed the relation between ITGB3 1565T/C (4G/4G) mutation and RPL [21–23], the analysis indicated that there was no increased risk of RPL associated with the ITGB3 1565T/C polymorphism, with an OR of 0.22 (95% CI: 0.15–0.30). The heterogeneity across studies was low ($I^2 = 15.7\%$, $P = 0.28$). In the Bayesian analysis, the corresponding log OR was estimated to be 0.35, with a 95% credible interval of 0.09 to 1.17, further suggesting no significant association between the ITGB3 1565T/C polymorphism and the risk of RPL.

The relation between Factor XIII Val 34 Leu mutation and recurrent pregnancy loss

Five studies examined the association between Factor XIII Val34Leu mutation and the risk of RPL [17,22,32,33,37]. The meta-analysis demonstrated a significant association between this mutation and an increased risk of RPL, with a pooled OR of 1.75 (95% CI: 1.23–2.50). No heterogeneity was observed across the included studies ($I^2 = 0\%$, $P = 0.976$). However, the Bayesian results support a potential association between Factor XIII Val34Leu mutation and an increased risk of RPL (corresponding log OR was 0.45, with 95% credible intervals, 0.05–0.95), though the lower credible interval suggests the possibility of a minimal or no effect.

The relation between the Factor V 5279 A/G mutation and recurrent pregnancy loss

Two studies assessed the association between Factor V 5279 A/G polymorphism and the risk of RPL [21,22]. The results demonstrated a significantly increased risk of RPL associated with this polymorphism, with a pooled OR of 7.5 and a 95% CI of 4.38–12.66. Minimal heterogeneity was observed between the studies ($I^2 = 15.7\%$, $P < 0.001$). The corresponding Bayesian log OR was 2.03, with 95% credible intervals of 1.25–2.80, supporting a significant association between the Factor V 5279 A/G polymorphism and elevated risk of RPL.

Table 3 Characteristics of studies including FVL G1691A, MTHFR C677T, MTHFR A1298C, MTHFR C677T + MTHFR A1298C, Prothrombin G20210A, PAI-1 (-675 I/D, 5G/4G), Factor V A4070G, Factor V 5279 A/G, β-fibrinogen (-455G/A), ACE (intron 16 I/D), ITGB3 1565T/C and, Factor XIII Val 34 Leu polymorphisms and recurrent pregnancy loss

First author (Ref)	Year	Number of cases	Number of controls	Genotypes		Number of events in patients (%)		Number of events in controls (%)		Lower limit		Upper limit		OR	
				Hetero	Homo	Hetero	Homo	Hetero	Homo	Hetero	Homo	Hetero	Homo	Hetero	Homo
FVL G1691A															
Farahmand *et al.* [14]	2015	330	350	Heterozygote		28 (8.48)		10 (2.85)		1.5		6.59		3.15	
Ardestani *et al.* [15]	2013	80	80	Heterozygote		2 (2.5)		1 (1.25)		0.18		22.7		1	
Pazoki *et al.* [16]	2019	100	100	Heterozygote		20 (20)		NA		0.42		32.86		2.09	
Zonouzi *et al.* [17]	2013	89	50	Heterozygote		2 (2.25)		0 (0)		0.991		1.056		1.023	
Zolfaghari *et al.* [18]	2020	60	60	Heterozygote		22 (36.6)		12 (20)		0.268		1.141		0.552	
Kardi *et al.* [19]	2018	250	116	Hetero	Homo	12 (5)	2 (0.8)	5 (4)	2 (1.7)	0.38	0.06	3.22	3.32	1.11	0.46
Khaniani *et al.* [20]	2017	210	160	Hetero	Homo	8 (3.8)	20 (96)	2 (1.25)	15 (98.75)	0.6	0.06	15	1.5	3	0.3
Torabi *et al.* [21]	2012	100	100	Heterozygote		13 (13)		4 (4)		1.443		33.177		6.92	
Bigdeli *et al.* [22]	2018	200	200	Heterozygote		50 (25)		8 (4)		3.68		17.39		8	
MTHFR C677T															
Farahmand *et al.* [14]	2015	330	350	Heterozygote		114 (34.54)		85 (24.20)		1.17		2.17		1.59	
Pazoki *et al.* [16]	2019	100	100	Heterozygote		28 (28)		N.A		1.53		33.97		7.14	
Zolfaghari *et al.* [18]	2020	60	60	Heterozygote		7 (11.6)		0		0.4634		2.338		1.077	
Bigdeli *et al.* [22]	2018	200	200	Heterozygote		109 (55)		61 (30.5)		1.81		4.11		2.729	
Jeddi-Tehrani *et al.* [23]	2011	100	100	Heterozygote		31 (31)		6 (6)		1.451		4.562		2.573	
Yousefian *et al.* [24]	2014	204	116	Hetero	Homo	90 (44.1)	18 (8.8)	43 (37.1)	10 (8.6)	0.84	0.51	2.22	2.72	1.37	1.18
Bagheri *et al.* [25]	2010	53	61	Hetero	Homo	22 (36.07)	5 (8.2)	21 (39.62)	5 (9.43)	0.4	0.23	1.84	1.84	0.86	0.86
Eskandari *et al.* [26]	2013	105	98	Hetero	Homo	48 (46)	14 (13)	30 (31)	7 (7)	1	0.7	3.3	5.2	1.9	2
MTHFR A1298C															
Farahmand *et al.* [14]	2015	330	350	Heterozygote		152 (46.06)		20 (6)		13.99		37.51		22.9	
Pazoki *et al.* [16]	2019	100	100	Heterozygote		30 (30)		10 (10)		1.62		36.49		8.16	
Zolfaghari *et al.* [18]	2020	60	60	Heterozygote		9 (28.4)		7 (20)		0.23		1.15		0.53	
Khaniani *et al.* [20]	2017	210	160	Homozygote		19 (9.04)		1 (0.62)		2		119		15.8	
Torabi *et al.* [21]	2012	100	100	Heterozygote		31 (31)		6 (6)		2.31		22.08		7.14	
Bigdeli *et al.* [22]	2018	200	200	Heterozygote		58 (29)		29 (14.5)		1.463		3.964		2.408	
Jeddi-Tehrani *et al.* [23]	2011	100	100	Heterozygote		31 (31)		6 (6)		2.783		17.79		7.039	
Yousefian *et al.* [24]	2014	204	116	Hetero	Homo	81 (39.7)	25 (12.3)	39 (33.6)	9 (7.8)	0.88	0.84	2.35	4.38	1.44	1.92
Bagheri *et al.* [25]	2010	53	61	Hetero	Homo	28 (45.9)	9 (14.75)	24 (45.28)	8 (15)	0.49	0.35	2.15	2.73	1.03	0.97
Eskandari *et al.* [26]	2013	105	98	Hetero	Homo	58 (47)	21 (20)	37 (38)	14 (14)	1.1	0.7	3.5	3.1	2	1.5
MTHFR C677T and MTHFR A1298C															
Farahmand *et al.* [14]	2015	330	350	Heterozygote		31 (9.39)		3 (0.85)		3.62		39.62		11.99	

Table 3 Continued.

Bagheri *et al.* [25]	2010	53	61	Heterozygote	10 (16.39)	7 (13.21)	0.45	3.66	1.28
Prothrombin G20210A Heterozygote									
Farahmand *et al.* [14]	2015	330	350	Heterozygote	14 (4.24)	10 (2.85)	0.65	3.44	1.5
Pazoki *et al.* [16]	2019	100	100	Heterozygote	20 (36)	N. A	0.16	36.49	1.79
Zonouzi *et al.* [17]	2013	89	50	Heterozygote	2 (2.24)	0 (0)	0.991	1.05	1.02
Kardi *et al.* [19]	2018	250	116	Heterozygote	15 (6)	1 (0.90)	1.16	66.6	8.81
Bigdeli *et al.* [22]	2018	200	200	Heterozygote	8 (4)	1(<1)	1.027	66.96	8.292
Bagheri *et al.* [27]	2011	70	60	Heterozygote	22 (31.42)	3 (5)	2.27	39.0	8.71
Isazadeh *et al.* [28]	2017	320	320	Heterozygote	6 (1.88)	5 (1.56)	0.371	50.11	1.09
Prothrombin G20210A Homozygote									
Bagheri *et al.* [27]	2011	70	60	Homozygote	48 (68.5)	57 (95)	0.03	0.44	0.11
Isazadeh *et al.* [28]	2017	320	320	Homozygote	314 (98.12)	315 (98.43)	0.14	9.901	1.455
Bagheri *et al.* [29]	2021	60	60	Homozygote	59 (98.3)	60 (100)	0.414	0.594	0.496
PAI-1 (-675 I/D, 5G/4G)									
Zonouzi *et al.* [17]	2013	80	59	Heterozygote	63 (70.79)	35 (70)	0.487	2.216	1.03
Zolfaghari *et al.* [18]	2013	60	60	Heterozygote	25 (42)	23 (38)	0.412	1.616	0.802
Bigdeli *et al.* [22]	2018	200	200	Heterozygote	130 (65)	50 (25)	3.616	8.585	5.571
JeddiTehrani *et al.* [23]	2011	100	100	Heterozygote	17 (17)	27 (27)	0.984	3.099	1.714
Bagheri *et al.* [29]	2021	60	60	Heterozygote	25 (41.6)	14 (23.3)	1.606	9.612	3.929
Shakarami *et al.* [30]	2015	100	100	Heterozygote	50 (50)	50 (50)	0.75	2.41	1.36
Khosravi *et al.* [31]	2013	421	100	Heterozygote	208 (49.4)	27 (27)	2.64	7.1	4.33
Khosravi *et al.* [31]	2013	251	100	Heterozygote	122 (48.6)	27 (30)	2.56	7.35	4.34
PAI-1 (4G /4G)									
Bagheri *et al.* [29]	2021	60	60	Homozygote	20 (33.33)	13 (21.6)	1.33	8.55	3.38
Shakarami *et al.* [30]	2015	100	100	Homozygote	17 (17)	5 (5)	1.55	13.84	4.63
Khosravi *et al.* [31]	2013	421	100	Homozygote	85 (20.2)	1 (1)	6.52	350.65	47.81
Khosravi *et al.* [31]	2013	251	100	Homozygote	54 (21.5)	1 (1)	6.99	384.69	51.84
Aarabi *et al.* [32]	2011	63	114	Homozygote	10 (15.8)	2 (1.7)	2.3	52.4	11
Soltangharaei *et al.* [33]	2005	120	112	Homozygote	16 (13.3)	2 (1.7)	1.62	36.49	8.16
Factor V A4070G									
Zonouzi *et al.* [17]	2013	89	50	Heterozygote	4 (4.49)	2 (4)	0.199	6.395	1.129
Bigdeli *et al.* [22]	2018	200	200	Heterozygote	14 (7)	4(2)	1.192	11.408	3.668
Arabkhazaeli *et al.* [34]	2016	100	100	Heterozygote	5 (5)	9 (9)	0.607	5.82	1.88
β-fibrinogen (-455G/A)									
Poursadegh Zonouzi *et al.* [17]	2013	89	50	Heterozygote	44 (49.43)	26 (52)	0.451	1.805	0.903
Zolfaghari *et al.* [18]	2013	60	60	Heterozygote	25 (42)	18 (30)	0.373	1.518	0.76
Torabi *et al.* [21]	2012	100	100	Heterozygote	33 (33)	11 (11)	1.97	13.798	5.213
Bigdeli *et al.* [22]	2018	200	200	Heterozygote	69 (34.5)	37 (18.5)	1.463	3.679	2.32
Jeddi-Tehrani *et al.* [23]	2011	100	100	Heterozygote	33 (33)	11 (11)	1.991	8.546	4.125
Maziri *et al.* [35]	2017	50	50	Heterozygote	17 (34)	20 (40)	0.475	1.203	0.756
Shokrzadeh *et al.* [36]	2019	101	50	Heterozygote	30 (29.7)	25 (50)	0.22	0.9	0.44
ACE (intron 16 I/D)									
Poursadegh Zonouzi *et al.* [17]	2013	89	50	Heterozygote	66 (56.74)	43 (58)	0.184	1.183	0.467
Shakarami *et al.* [30]	2015	100	100	Heterozygote	60 (60)	48 (48)	1.57	9.63	1.68
Maziri *et al.* [35]	2017	50	50	Heterozygote	13 (26)	22 (44)	1.207	3.284	1.991
ITGB3 1565T/C									
Torabi *et al.* [21]	2012	100	100	Heterozygote	1 (1)	27 (27)	0.051	0.319	0.127
Jeddi-Tehrani *et al.* [23]	2011	100	100	Heterozygote	27 (27)	17 (17)	0.159	0.579	0.303
Factor XIII Val 34 Leu									
Poursadegh Zonouzi *et al.* [17]	2013	89	50	Homozygote	30 (33.7)	12 (24)	0.735	3.526	1.61
Bigdeli *et al.* [22]	2018	200	200	Homozygote	79 (39.5%)	54 (27%)	1.158	2.691	1.765
Isazadeh *et al.* [28]	2017	320	320	Homozygote	14 (4.37)	13 (4.06)	0.139	6.133	1.501
Aarabi *et al.* [32]	2011	63	114	Homozygote	2 (3.17)	1 (0.8)	0.3	43.5	3.9
Soltangharaei *et al.* [33]	2005	120	112	Homozygote	2 (1.7)	1 (0.9)	0.16	20.09	1.79
Factor V 5279 A/G									
Torabi *et al.* [21]	2012	100	100	Heterozygote	36 (36)	7 (7)	2.323	18.206	6.503
Bigdeli *et al.* [22]	2018	200	200	Heterozygote	71 (35.5%)	13 (6.5%)	4.206	14.9	7.917

ACE, angiotensin-converting enzyme; FVL, Factor V Leiden; Hetero, heterozygote; Homo, homozygote; ITGB3, integrin beta-3; Leu, leucine; MTHFR, methylenetetrahydrofolatereductase; NA, not available; OR, odds ratio; PAI-1, plasminogen activator inhibitor; RPL, recurrent pregnancy loss; Val, valine.

Preeclampsia

Two studies evaluated the correlation between thrombophilia gene polymorphism and preeclampsia in the heterozygote and homozygote models [38,39]. The details of the studies are presented in Table 4.

The relation between the Factor V Leiden G1691A mutation and preeclampsia

Two studies assessed the association between the FVL G1691A mutation and the risk of preeclampsia [38,39]. The findings indicated no significant association between

Table 4 Characteristics of studies including FVL G1691A polymorphisms and preeclampsia

First author (Ref)	Year	Number of cases	Number of controls	Genotypes	Number of events in patients (%)	Number of events in controls (%)	Lower Limit	Upper Limit	OR
FVL G1691A									
Malek Khosravi *et al.* [38]	2011	198	101	Heterozygote	15 (7.5)	8 (7.9)	0.39	2.3	0.95
Karimi *et al.* [39]	2011	198	201	Heterozygote	17 (8.6)	2 (1)	2.12	41.01	9.34

FVL, Factor V Leiden; Hetero, heterozygote; Homo, homozygote; OR, odds ratio.

this mutation and an increased risk of preeclampsia, with a pooled OR of 2.75 (95% CI: 0.29–25.68), suggesting high uncertainty. Moreover, significant heterogeneity was observed between the studies ($I^2 = 85.1\%$, $P = 0.009$). The corresponding log OR (95% credible intervals) was 0.74 (−0.45–2.06) for FVL G1691A.

Venous thromboembolism

Considering that DVT is a subgroup of VTE, we included studies that assessed the association between thrombophilia-related gene mutations and DVT in a meta-analysis comprising six studies [10–12,40–42]. It should also be noted that portal vein thrombosis (PVT) was classified as a type of VTE in our study. The detailed results are presented in Table 5.

The relation between heterozygosity for the Factor V Leiden G1691A mutation and venous thromboembolism

Four studies reported the association between FVL G1691A heterozygote mutation and VTE [10–12,40]. The results showed that this mutation significantly increased the risk of VTE (OR: 4.26, 95% CI: 2.19–8.30), with no heterogeneity observed ($I^2 = 0\%$, $P = 0.585$). The corresponding log OR for FVL G1691A heterozygote with 95% credible intervals was found to be 1.88 (1.04–2.72).

The relation between heterozygosity for the MTHFR C677T mutation and venous thromboembolism

Three studies assessed the relation between MTHFR C677T heterozygote mutation and VTE [40–42]. The results suggest that this mutation increased the risk of VTE (OR: 1.404, 95% CI: 1.030–1.914); also, there was no heterogeneity among the studies ($I^2 = 0\%$, $P = 0.602$). The corresponding log OR (95% credible interval) was 0.91 (−0.25–2.15) for MTHFR C677T heterozygote.

Table 6 summarizes the main findings of the meta-analysis evaluating the association between various gene polymorphisms and thrombotic disorders in the Iranian population.

Table 5 Characteristics of studies included in FVL G1691A, and MTHFR C677T polymorphisms and VTE

First author/Ref	Year	Number of cases	Number of controls	Genotypes	Number of events in patients (%)	Number of events in controls (%)	Lower limit	Upper limit	OR
FVL G1691A									
Rahimi [10]	2010	80	100	Heterozygote	7 (11.4)	2 (2)	1.32	30.05	6.3
Hosseini [11]	2015	182	250	Heterozygote	18 (9.9)	4 (1.6)	2.2	20.03	6.7
Karimi [12]	2015	35	306	Heterozygote	2 (5.7)	0 (0)	0.52	12.98	2.59
Pourgheysari [40]	2013	35	306	Heterozygote	4 (11.4)	7 (2.2)	0.72	8.83	2.51
MTHFR C677T									
Pourgheysari [40]	2013	35	306	Heterozygote	32 (91.4)	110 (35.9)	0.85	2.4	1.43
Soltanpour [42]	2008	200	100	Heterozygote	68 (34)	37 (37)	0.83	1.94	1.27
Ghaznavi [41]	2015	10	80	Heterozygote	5 (50)	30 (37.5)	0.73	4.66	2.14

FVL, Factor V Leiden; Hetero, heterozygote; Homo, homozygote; MTHFR, methylene tetra hydro folate reductase; OR, odds ratio; VTE, venous thrombo embolism.

Table 6 The meta-analysis of thrombophilic gene polymorphisms and various clinical picture risks in the Iranian Population

Polymorphism	Clinical picture	Number of studies	Genetic model	Type of model	Heterogeneity		Odds ratio				Bayesian Meta	
					I^2(%)	Q	OR	95% CI	Z_{test}	P_{OR}	Mean	95% CI
FVL G1691A	CVST	2	Heterozygote	Random	88.2	0.004	1.822	0.076–43.934	0.369	0.712	1.74	0.17–3.29
	DVT	3	Heterozygote	Fixed	0	0.612	5.255	2.393–11.541	4.134	<0.001	1.95	0.92–3
	RPL	9	Heterozygote	Random	82.7	<0.001	1.998	1.026–3.888	2.036	0.042	1.13	0.60–1.65
	RPL	2	Homozygote	Fixed	0	0.742	0.356	0.102–1.239	−1.623	0.104	−0.97	−2.33–0.40
	VTE	4	Heterozygote	Fixed	0	0.585	4.265	2.190–8.303	4.266	<0.001	1.88	1.04–2.72
	Preeclampsia	2	Heterozygote	Random	85.1	0.009	2.749	0.294–25.68	0.887	0.375	0.74	−0.45–2.06
MTHFR C677T	CVST	3	Heterozygote	Random	65.3	0.056	1.029	0.456–2.325	0.069	0.945	0.52	−0.12–1.16
	CVST	3	Homozygote	Random	63.7	0.064	1.031	0.366–2.904	0.058	0.954	0.65	−0.09–1.39
	DVT	4	Homozygote	Random	75	0.007	1.735	0.884–3.407	1.602	0.109	0.45	−0.28–1.24
	RPL	8	Heterozygote	Random	54.8	0.030	1.778	1.318–2.398	3.770	<0.001	0.73	0.32–1.21
	RPL	4	Homozygote	Fixed	2.4	0.380	1.058	0.657–1.704	0.232	0.817	0.06	−0.55–0.69
	VTE	3	Heterozygote	Fixed	0	0.602	1.404	1.030–1.914	2.149	0.032	0.91	−0.25–2.15
MTHFR A1298C	DVT	2	Heterozygote	Random	81.7	0.019	3.107	0.336–28.692	0.999	0.318	1.01	−0.29–2.30
	RPL	9	Heterozygote	Random	92.7	<0.001	3.102	1.335–7.208	2.631	0.009	1.17	0.61–1.72
	RPL	4	Homozygote	Fixed	49.3	0.116	1.685	1.050–2.704	2.164	0.030	0.59	−0.05–1.27
MTHFR C677T and MTHFR A1298C	RPL	2	Heterozygote	Random	86.8	0.006	3.856	0.434–34.28	1.210	0.226	1.43	0.25–2.62
Prothrombin G20210A	RPL	7	Heterozygote	Random	66.4	0.007	2.435	1.099–5.398	2.191	0.028	1.04	0.31–1.84
	RPL	3	Homozygote	Fixed	65.3	0.056	0.487	0.407–0.582	−7.918	<0.001	−1.11	−2.23–0
PAI-1 (−675 I/D, 5G/4G)	RPL	7	Heterozygote	Random	85.2	<0.001	2.138	1.184–3.858	2.521	0.012	0.6	0–1.18
PAI-1 (4G/4G)	RPL	5	Homozygote	Fixed	53.1	0.058	7.087	4.094–12.269	6.993	<0.001	1.73	0.98–2.57
Factor V A4070G	RPL	3	Heterozygote	Fixed	0	0.491	2.266	1.097–4.682	2.209	0.027	0.29	−0.71–1.28

Table 6 Continued.

Polymorphism	Clinical picture	Number of studies	Genetic model	Type of model	Heterogeneity		Odds ratio				Bayesian Meta	
					I^2(%)	*Q*	OR	95% CI	Z_{test}	P_{OR}	Mean	95% CI
β-fibrinogen (−455G/A)	RPL	7	Heterozygote	Random	82.6	<0.001	1.519	0.744–3.10	1.148	0.251	0.42	−0.2–1.03
ACE (intron 16 I/D)	RPL	3	Heterozygote	Random	72.7	0.026	1.228	0.525–2.872	0.474	0.636	−0.23	−1.11–0.56
ITGB3 1565T/C	RPL	2	Heterozygote	Fixed	15.7	0.305	0.216	0.151–0.308	−8.437	<0.001	−1.05	−2.36–0.17
Factor XIII Val 34 Leu	RPL	5	Homozygote	Fixed	0	0.976	1.751	1.226–2.501	3.078	0.002	0.45	−0.05–0.95
FV 5279 A/G	RPL	2	Heterozygote	Fixed	0	0.750	7.502	4.376–12.858	7.329	<0.001	2.03	1.25–2.80

ACE, angiotensin-converting enzyme; CI, confidence interval; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; FVL, Factor V Leiden; ITGB3, integrin beta 3; Leu, leucine; MTHFR, methylenetetrahydrofolate reductase; OR, odds ratio; PAI-1, plasminogen activator inhibitor-1; RPL, recurrent pregnancy loss; Val, valine; VTE, venous thromboembolism.

The figures of the Bayesian Meta-analysis and Random/fixed effect Meta-analysis were presented in the Data Supplementary file, http://links.lww.com/BCF/A191.

Discussion

This meta-analysis encompasses findings from 36 studies, analyzing over 14 000 cases and controls to explore the correlation between inherited thrombophilia and specific gene polymorphisms associated with thrombotic disorders in the Iranian population. Twelve polymorphisms across eight genes were investigated, including MTHFR C677T, MTHFR A1298C, prothrombin G20210A, FVL G1691A, FV A4070G, FV 5279 A/G, PAI-1 4G/5G, PAI-1 (-675 I/D, 5G/4G), PAI-1 4G/4G, β-fibrinogen (−455G/A), ACE (intron 16 I/D), ITGB3 1565T/C, and FXIII Val34Leu. These genetic variants were identified as significant contributors to the development of five thrombotic conditions: CVST, VTE, DVT, RPL, and preeclampsia. Our research has identified various genetic polymorphisms linked to an increased risk of RPL in the Iranian population. These genetic variations include FVL G1691A heterozygote, MTHFR C677T heterozygote, MTHFR A1298C (in both homozygous and heterozygous forms), prothrombin G20210A (in both homozygous and heterozygous forms), PAI-1 (−675 I/D, 5G/4G), PAI-1 homozygous (4G/4G), FVA4070G, Factor V 5279 A/G, factor XIII Val34Leu, and ITGB3 1565T/C polymorphisms. These results are consistent with previous meta-analyses, further underscoring the role of these genetic variations in the development of RPL.

Kamali *et al.* similarly identified significant correlations between various genetic polymorphisms, including MTHFR C677T, MTHFR A1298C, prothrombin G20210A, FVL G1691A, and PAI-1 4G/5G, and risk of RPL within the Iranian population. Their findings highlight the potential role of these genetic variants in influencing susceptibility to RPL, contributing to a deeper understanding of its underlying etiology [43]. The findings of our study are consistent with previous research conducted in Chinese populations, which demonstrated a significant association between the MTHFR C677T polymorphism, in both homozygous and heterozygous states, and RPL [44].

The MTHFR C677T polymorphism has been identified as a potential risk factor for RPL in Asian populations, according to various studies. However, this association has not been observed in Caucasian populations, suggesting potential ethnic or genetic differences in susceptibility [45,46]. Nevertheless, inconsistencies and conflicting findings are evident in the existing literature. Our research aligns with the findings of Nair *et al.*'s meta-analysis [47], which identified MTHFR A1298C as a risk factor for RPL. However, it is essential to note that Cao *et al.* did not observe this association in their study [46].

Regarding other genetic variations, we have observed a correlation between specific polymorphisms such as PAI-1 homozygote (4G/4G), FV A4070G, FV 5279 A/G, FXIII Val 34 Leu, and ITGB3 1565T/C with the risk of RPL. A meta-analysis by Gao *et al.* reported that the prothrombin G20210A variant increases the risk of RPL, especially in European women over 29 years old ($OR_{RPL} = 1.81$, $P < 0.05$) [48]. However, previous meta-analyses have yielded inconsistent results, which can likely be attributed to limitations such as small sample sizes.

A literature review by Monash University's Department of Obstetrics and Gynaecology analyzed six case-control studies on the link between the prothrombin G20210A mutation and RPL, encompassing 323 affected women, using Medline data from 1966 to 2000. The OR for heterozygous mutation was 1.9 (95% CI: 0.98–4.14), while homozygous mutation showed an OR of 3.76 (95% CI: 0.75–18.77). Despite potential trends suggesting increased risk, the study found insufficient evidence to confirm a definitive association [49]. A meta-analysis conducted by the Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, and the Center for Clinical Epidemiology and Biostatistics at the University of Pennsylvania reported that carriers of Factor V Leiden or prothrombin gene mutations have approximately twice the risk of experiencing two or more miscarriages compared to women without these hereditary thrombophilias [50]. In another meta-analysis with the aim of cost-effectiveness analysis, screening for thrombophilia in high-risk situations was performed, which reached an OR of 2.70 for early RPL and 8.60 for late RPL [51].

In another meta-analysis from Canada, which included 31 case-control, cohort, and cross-sectional studies, FVL was associated with early and late recurrent fetal loss, as well as late nonrecurrent fetal loss. In addition, prothrombin

G20210A mutation was associated with early recurrent (2.56, 1.04-.29) and late nonrecurrent (2.30, 1.09–4.87) fetal loss [52].

A systematic review and meta-analysis conducted in China in 2021 included a total of 89 studies, comprising 30 254 individuals. The findings revealed that women carrying the FVL mutation or experiencing a deficiency in Protein S had a significantly increased risk of developing RPL. In contrast, no significant association was observed between antithrombin deficiency, protein C deficiency, and the risk of RPL (all *P*-values > 0.05). The observed heterogeneity in risk estimates for RPL was partially explained by factors such as geographic region, definitions of RPL, types of RPL, and the extent to which studies controlled for confounding variables [53]. As a result, numerous studies have shown a significant association between this genetic mutation and an increased likelihood of RPL, highlighting its importance in understanding and managing pregnancy complications [54–57].

The meta-analysis highlights a significant association between PAI-1 4G/5G polymorphism and RPL. Chen *et al*. conducted a systematic review of 18 studies, revealing that despite notable statistical heterogeneity, the PAI-1-4G/A polymorphism is associated with an increased risk of RPL under the recessive model, with an OR of 1.70 (95% CI: 1.21–2.38) [58].

A systematic review analyzed published literature from the MEDLINE and EMBASE databases up to April 2012, focusing on the association between gene polymorphisms and RPL. Out of 209 identified studies, 22 case-control studies were selected, involving a total of 2820 RPL patients and 3009 controls. Among these, 11 studies specifically investigated the PAI-1 4G/5G polymorphism in RPL patients. Despite this, substantial clinical heterogeneity was noted across the studies, and the pooled analysis did not demonstrate a significant association between the PAI-1 4G/5G polymorphism and increased susceptibility to idiopathic RPL. The authors recommended that future research should focus on well designed, large-scale studies conducted across diverse ethnic populations to provide more definitive conclusions [59]. Another meta-analysis from China has suggested that PAI-1 4G/5G polymorphism might be associated with RPL development in Caucasians [60].

In the current analysis, no association was found between FVL G1691A and MTHFR C677T polymorphisms, whether homozygous or heterozygous, and the development of CVST in the Iranian population. However, our findings contradict the results of previous meta-analysis studies. A systematic review, including cohort studies with 40 or more patients and case-control studies, was conducted to compare the prevalence of thrombophilia in patients with CVST and unrelated control groups. Overall, 18 studies evaluating the role of the FVL mutation for the risk of CVST included 919 cases and 3168 healthy controls. In comparison with controls, the pooled OR for CVST was 2.89 (95% CI: 2.10–3.97; $P < 0.001$). The results demonstrated a significant association between CVST and all major inherited thrombophilic factors, as well as elevated homocysteine levels. However, the available evidence regarding the role of thrombophilia in the risk of recurrent CVST or other forms of VTE remained inconclusive [61]. A Canadian meta-analysis encompassing seventeen studies has found a significant association between factor V Leiden and an elevated risk of CVST. The OR was calculated at 3.38, with a 95% CI ranging from 2.27 to 5.05, and the results were statistically significant ($P < 0.001$) [62].

A study was conducted to assess the impact of thrombophilia on the risk of a first childhood stroke through a meta-analysis of published observational studies. A systematic search of electronic databases identified relevant studies published between 1970 and 2009. The analysis included a total of 1764 pediatric stroke patients: 1526 with arterial ischemic stroke and 238 with CSVT, as well as 2799 control subjects ranging from neonates to 18 years of age. No significant heterogeneity was observed across the included studies. The meta-analysis demonstrated a statistically significant association between various hereditary thrombophilia traits and the risk of a first stroke in children, with no significant difference in risk estimates between AIS and CSVT. The pooled OR with 95% CI for each thrombophilia trait were as follows: Antithrombin deficiency: OR = 7.06 (95% CI: 2.44–22.42), Protein C deficiency: OR = 8.76 (95% CI: 4.53–16.96), Protein S deficiency: OR = 3.20 (95% CI: 1.22–8.40), Factor V G1691A mutation: OR = 3.26 (95% CI: 2.59–4.10), Prothrombin G20210A mutation: OR = 2.43 (95% CI: 1.67–3.51), MTHFR C677T polymorphism (AIS only): OR = 1.58 (95% CI: 1.20–2.08) and Combined thrombophilias: OR = 11.86 (95% CI: 5.93–23.73). These findings indicated that the majority of hereditary thrombophilias are significant risk factors for the development of stroke in children [63].

VTE can be presented as DVT or pulmonary embolism. Various genetic and environmental risk factors influence its development and progression. Some notable genetic factors include mutations such as FVL G1691A, MTHFR C677T, MTHFR A1298C, and Prothrombin G20210A. These mutations can increase the likelihood of clot formation, contributing to the complexity of VTE [64]. Our findings indicated that there was a weak association between MTHFR C677T heterozygote polymorphism and an increased incidence of VTE in the Iranian population (OR: 1.40, 95% CI: 1.03–1.914), while FVL G1691A heterozygote polymorphism significantly increased the risk of VTE in this population (OR:4.265, 95% CI: 2.19–8.30).

An extensive meta-analysis examined the relationship between genetic factors and VTE risk in adults, utilizing data from over 11 000 cases and 21 000 controls. It focused on FVL, Prothrombin 20210A, and MTHFR C677T. Findings showed no significant link between homozygous MTHFR C677T and VTE risk (OR: 1.38; 95% CI:

0.98–1.93). In contrast, VTE risk was notably higher in heterozygous carriers of FVL (OR: 4.22; 95% CI: 3.35–5.32) and Prothrombin G20210A (OR: 2.79; 95% CI: 2.25–3.46) and further increased in double heterozygotes (OR: 3.42; 95% CI: 1.64–7.13). The most significant risk appeared in homozygous FVL (OR: 11.45; 95% CI: 6.79–19.29) and Prothrombin G20210A carriers (OR: 6.74; 95% CI: 2.19–20.72). The study highlights the significantly increased risk of VTE in individuals with combined genetic variants [65].

A meta-analysis conducted in Italy in 2022 explored the association between inherited thrombophilia and VTE in individuals with non-O blood types, drawing on data from 17 studies encompassing over 152 000 patients. The research evaluated the combined effects of FVL and Prothrombin G20210A mutations alongside non-O blood groups. The simultaneous presence of FVL and a non-O blood type significantly increased the risk of VTE (OR 5.94, 95% CI 5.33–6.61; $P < 0.01$), surpassing the risk associated with each factor alone. Likewise, Prothrombin G20210A, paired with a non-O blood group, also elevated the VTE risk (OR 4.01, 95% CI 3.00–5.36; $P = 0.01$), albeit with a lower population-attributable risk (PAR: 3.7%). The findings highlight the increased risk associated with the interaction between genetic factors and blood type [66].

To evaluate the role of the MTHFR 677 TT homozygous genotype in the risk of VTE, a meta-analysis was conducted at the Sunnybrook and Women's College Health Sciences Center in Toronto. Data from 31 studies, involving 4901 VTE cases and 7886 controls, revealed that the prevalence of the MTHFR 677 TT genotype was slightly higher in cases (14.3%) compared to controls (11.7%). This genotype conferred a marginally increased risk of VTE, as indicated by the odds ratio analysis. However, the findings suggested that the association between hyperhomocysteinemia and VTE is unlikely to be primarily mediated by this gene polymorphism. Other unidentified genetic factors may better explain this relationship. In conclusion, while the MTHFR C677T polymorphism shows a weak association with an increased risk of VTE, its overall impact appears to be limited [67].

The results of our meta-analysis showed no association between FVL G1691A and increased risk of Preeclampsia (OR: 2.749, 95% CI: 0.29–25.68). A meta-analysis conducted at Brigham and Women's Hospital, Harvard Medical School, investigated the association between specific genetic polymorphisms and the risk of preeclampsia. The study analyzed data from 31 studies, encompassing a total of 7522 patients. It focused on three genetic factors: FVL1691GA, single-nucleotide polymorphism (SNP), MTHFR 677 C–T SNP, and the prothrombin 20210 G-A SNP. Notably, data from patients with severe preeclampsia were separately extracted and analyzed to provide a more detailed understanding. The meta-analysis findings indicated that the FVL SNP was strongly linked to an elevated risk of preeclampsia development, differing from the results of our analysis [68].

A meta-analysis in China examined the link between thrombophilia gene polymorphisms and preeclampsia. Analyzing data from 37 studies involving 5048 preeclampsia patients and 6796 controls, researchers found significant associations. The prothrombin G20210A polymorphism was linked to a higher risk of preeclampsia overall (OR = 1.81, 95% CI: 1.25–2.63) and severe preeclampsia (OR = 3.02, 95% CI: 2.06–4.45). Similarly, the FVL polymorphism was associated with an increased risk for all preeclampsia cases (OR = 1.60, 95% CI: 1.28–2.00) and severe cases (OR = 2.45, 95% CI: 1.63–3.69). These findings suggest that the FVL SNP and prothrombin G20210A SNP contribute to elevated risks for both general and severe preeclampsia, emphasizing their potential role in the condition's pathology [69].

Overall, this meta-analysis highlights the role of genetic polymorphisms in thrombophilia among Iranian populations, emphasizing the importance of targeted genetic testing to optimize the diagnosis and management of thrombotic disorders. For Iranian patients with RPL, testing for MTHFR C677T and A1298C mutations is recommended, potentially reducing costs and unnecessary interventions by avoiding broad thrombophilia panels. In cases of CVST, first-line testing for FVL G1691A and prothrombin G20210A mutations may not be essential. Similarly, routine screening for FVL G1691A or MTHFR mutations is not advised for initial preeclampsia diagnostics. For unprovoked VTE, genetic tests for prothrombin G20210A or MTHFR variants may not significantly impact clinical outcomes or treatment decisions. However, in Iranian patients with unprovoked or recurrent DVT, testing for MTHFR variants and FVL G1691A could improve treatment strategies and secondary prevention. Routine testing for prothrombin G20210A in DVT cases is unlikely to enhance clinical care significantly. A more focused approach involving FVL and MTHFR variants is suggested for diagnosing and managing DVT in Iranian patients, ensuring a more cost-effective and clinically relevant strategy.

To date, no studies have been conducted to investigate thrombophilia gene polymorphisms in the Iranian population regarding RPL, CVST, VTE, DVT, and preeclampsia. Nevertheless, it is essential to acknowledge certain limitations when interpreting the findings of this meta-analysis.

Limitations

This meta-analysis highlights several limitations that must be considered to accurately interpret its findings. Firstly, the investigation into the association between thrombophilia genes and preeclampsia or CVST in Iranian patients was constrained by the limited number of relevant studies. Secondly, only published studies were included, potentially excluding significant unpublished research that met the inclusion criteria. Thirdly, the

diverse ethnic composition of the Iranian population, such as Persian, Azeri, Kurdish, and others, could not be analyzed due to insufficient subgroup data from primary studies. Fourthly, publication bias and sensitivity analyses were not feasible due to the limited number of eligible studies per polymorphism and thrombosis. Additionally, the study focused only on heterozygosity or homozygosity, without considering specific alleles. It also relied solely on studies reported OR with 95% CI. Lastly, the quality and sample sizes of the included studies were limited, emphasizing the need for future research with larger, more diverse cohorts to address these shortcomings. These limitations underscore the importance of cautious interpretation and the necessity for further comprehensive investigations in this area.

Conclusion

This meta-analysis involving over 14 000 Iranian patients sheds light on the impact of inherited thrombophilia gene polymorphisms on thrombotic disorders. It highlights several genetic mutations associated with an increased risk of specific conditions. For RPL, mutations such as FVL G1691A heterozygote, MTHFR C677T heterozygote, MTHFR A1298C (both homozygote and heterozygote), prothrombin G20210A (both homozygote and heterozygote), PAI-1 polymorphisms, FV A4070G, FV 5279A/G, FXIII Val34Leu, and ITGB3 1565T/C were found to elevate risk.

This study investigates the genetic factors influencing thrombotic disorders in the Iranian population, specifically examining the connection between the FVL G1691A heterozygote mutation and VTE, and the MTHFR C677T heterozygote mutation and DVT. No significant links were found between these polymorphisms and CVST or preeclampsia. It advocates testing for FVL G1691A, prothrombin G20210A, MTHFR C677T, and A1298C mutations to assess the risk of RPL and highlights the importance of FVL G1691A screening for DVT. However, routine thrombophilia panels may be of limited diagnostic value for CVST or preeclampsia. Providing a basis for a cost-effective, tailored approach to managing thrombophilia, the findings call for further research to enhance diagnostic methods within this population, advancing prevention and treatment strategies in Iran.

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Conflicts of interest

The authors declared no conflict of interest in this study.

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