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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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HEMOSTASIS GENE POLYMORPHISM IN RETINAL VASCULAR OCCLUSION: A SYSTEMATIC REVIEW

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Abstract.

Purpose: Retinal vascular occlusion (RVO), a common reason for vision loss, is divided into central and branch RVO. Although age, hypertension, and diabetes are established risk factors, genetic variations in hemostasis-related genes like Prothrombin G20210A, Factor V Leiden, and MTHFR may also contribute. Yet, there is conflicting evidence connecting these genetic variations to RVO. The objective of this research is to conduct a thorough evaluation and examination of the connection between variations in hemostasis genes, such as MTHFR C677T and A1298C, and retinal vessel occlusion.

Methods: A comprehensive review and meta-analysis were performed adhering to PRISMA standards. Databases (PubMed, Google Scholar, Ovid, Wiley) were queried for English-language studies (2018–2024) using keywords: "retinal vessel occlusion," "hemostasis genes," "thrombophilia," "Prothrombin G20210A," "Factor V Leiden," and "MTHFR polymorphism." This study included ten studies (n=2281 patients) that were published from 2019 to 2024. The level of heterogeneity for each polymorphism was determined utilizing a random-effects model, while quality of assessment was done using Cochrane risk of bias tool.

Results: There was no notable link observed between the MTHFR C677T polymorphism and RVO (P=0.90, OR=0.77, 95% CI=0.55–1.18, I2=0%). Equivalent findings were recorded for A1298C (P=0.84, OR=0.93, 95% CI=0.48–1.81, I2=27%) and MMP2-1306C/T (P=0.10, OR=0.70, 95% CI=0.41–1.20, I2=68%). Though there is some evidence linking polymorphisms in hemostasis genes like MTHFR C677T, A1298C, and others to hypercoagulable conditions, their connection to retinal vessel occlusion is still uncertain.

Conclusion: Some individual studies suggested a role for MTHFR polymorphisms in RVO, our meta-analysis found no significant association between these genetic variants and RVO risk.

This underscores the need for further research to clarify the interplay of genetic and environmental factors in RVO pathogenesis.

Key words. Retinal vein occlusion, hemostasis gene polymorphism, hyperhomocysteinemia, thrombophilic mutations.

Introduction.

Research Problem:

One of the main causes of vision loss in the globe is vascular occlusion in the retina [1]. Retinal artery occlusion (RAO) or retinal vein occlusion (RVO) are the two possible manifestations of this disorder. The two varieties are further divided into central RAO, branch RAO, central RVO (CRVO), and branch RVO (BRVO) according to the location of the blockage. Thromboembolic events, which impair blood flow in the retinal vessels, are the main cause of these disorders. According to estimates, between 0.1% and 0.4% of people have CRVO, and between 0.6% and 1.2% of people have BRVO. The significance of these vascular disorders on eye health worldwide is still being highlighted by recent research, which also stress the need of early detection and treatment to avoid permanent vision loss [2,3]. Modifiable and non-modifiable risk factors [4], including age, diabetes, hypertension, and dyslipidemia, have an impact on the complex pathophysiology of retinal vascular occlusion [5,6]. Because hypercoagulable states increase the probability of thrombus formation, they have been shown to be important factors to the development of both RAO and RVO in various populations. A higher risk of retinal vein occlusion has been linked to genetic abnormalities in clotting factors, such as mutations in Factor V Leiden and Prothrombin G20210A. In particular, people may be at risk for these vascular events if they have abnormalities in the genes that control coagulation factors like Factor II (Prothrombin) and Factor V as well as natural anticoagulants like protein C (PC), antithrombin III (AT-III), and protein S (PS) [7,8]. Furthermore, genetic differences in coagulation pathways have been connected to aberrant venous thromboembolism that occurs in places other than the lower limbs [9]. However, research on the importance of both acquired (like antiphospholipid antibody syndrome) and inherited (like Factor V Leiden mutation and Prothrombin G20210A mutation) conditions in the development of retinal vascular occlusions is still ongoing, with conflicting findings [10,11].

Research Focus:

Hemostasis is a carefully controlled mechanism that includes the coordination of vascular endothelial cells, platelets, and coagulation factors [12,13]. Genetic differences in important clotting genes can disrupt this equilibrium, resulting in either too much bleeding or clot formation [14-16]. Many clotting diseases, including deep vein thrombosis, stroke, and even retinal vein occlusion (RVO), have been linked to polymorphisms including Factor V Leiden (FVL), Prothrombin G20210A, and Methylenetetrahydrofolate reductase (MTHFR) C677T. These genetic differences may raise the chance of aberrant blood clot development, which can lead to vascular issues in the retina and other regions of the body [17,18]. In certain instances, these mutations might be present alongside other common health

issues, leading to a higher likelihood of venous blockages. Despite numerous studies and their findings, the mystery surrounding the causes of venous occlusion remains unresolved as of now [19]. RVO may develop because of hypercoagulation caused by certain mutations and polymorphisms in genes that control hemostatic balance, such as FV G1691A, FV G4070A, and FIIG 20210A, as well as factors related to endothelial function and integrity, fibrinolysis, and clot stability. Furthermore, hyperhomocysteinemia should be taken into account since changes in the genes that encode the enzymes that metabolize homocysteine, such as MTHFR C677T and A1298C, might result in decreased enzyme activity, which raises the risk of RVO [19,20]. One of the factors examined in this research was the MTHFR gene variation. A deficiency in MTHFR activity can lead to hyperhomocysteinemia and potentially raise the chances of developing blood clots in individuals who lack folic acid. Two common substitutions, C677T and A1298C, result in reduced MTHFR activity, leading to the enzyme becoming thermolabile. Studies and meta-analysis have emphasized a link between RVO and high levels of homocysteine. It is notable that 80.3% of the patients had at least one impacted MTHFR allele, suggesting a possible role for MTHFR in the development of RVO, even if the study by Giannaki et al. [19] reported no significant difference in the frequency of MTHFR polymorphisms between RVO patients and controls. Thymine (T) is substituted for cytosine (C) at nucleotide 677 in the single nucleotide polymorphism (SNP) C677T, which is found in the active area of the MTHFR enzyme. The alanine-to-valine conversion that follows creates a thermolabile MTHFR protein with decreased enzymatic activity. Homocysteine metabolism may be hampered by this decreased activity, which might exacerbate vascular occlusive diseases like RVO [21-23]. People who have the T allele in either homozygous or heterozygous form exhibit enzyme activity of the protein at 30% or 65%, respectively. This can result in elevated levels of plasma homocysteine (hyperhomocysteinemia), especially when folate levels in the bloodstream are low [21,24]. It is worth noting that elevated levels of homocysteine have been associated with vascular diseases [25], including RVO [26]. As an alternative, the A1298C polymorphism substitutes cytosine (C) for adenine (A), which causes glutamate to be replaced with alanine in the MTHFR enzyme's C-terminal regulatory domain. Although it has a less noticeable effect than the C677T mutation, this single nucleotide polymorphism (SNP) is likewise linked to decreased MTHFR function [27]. According to the research, the T allele in SNP C677T and the C allele in SNP A1298C are regarded as "risk variants" since they may contribute to vascular disorders such RVO and lower MTHFR enzyme activity.

Hypotheses:

Genetic polymorphisms in key clotting genes, such as Factor V Leiden, Prothrombin G20210A, and MTHFR (C677T and A1298C), are associated with an increased risk of retinal vascular occlusion (RVO) by contributing to hypercoagulability and elevated homocysteine levels, which impair normal blood flow in the retinal vessels.

Research Aim:

Despite the increasing amount of research on how hemostatic gene polymorphisms influence thrombotic diseases, there is still no agreement on the relationship between these genetic variations and retinal vessel occlusion. This review seeks to methodically evaluate the existing literature on the link between variations in clotting genes and RVO, offering a thorough analysis of the current proof and identifying gaps for future studies.

Research Questions:

1. What is the prevalence of key genetic polymorphisms (Factor V Leiden, Prothrombin G20210A, MTHFR C677T, A1298C) among individuals with retinal vascular occlusion (RVO), and how do these contribute to hypercoagulability and thromboembolic events?
2. Is there a significant association between MTHFR polymorphisms, elevated homocysteine levels, and an increased risk of retinal vein occlusion (RVO)?
3. How do genetic clotting risk factors (e.g., Factor V Leiden, Prothrombin G20210A) interact with modifiable risk factors (e.g., age, diabetes, hypertension) in influencing the development and prognosis of RVO?.

Methods.

Search Strategy:

An extensive search was conducted in various online literature databases such as PubMed, Google Scholar, Ovid, and Wiley, to find English-language full-text publications released from 2018 to 2024. Cochrane formulated the research question in accordance with the standards set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A comprehensive search plan was created by merging MeSH terms and relevant keywords from the literature. Keywords such as "retinal vessel occlusion", "hemostasis genes", "thrombophilia", "Prothrombin G20210A","Factor V Leiden", and "MTHFR polymorphism" were used in the search criteria. A method of cross-referencing was employed to find additional related studies by investigating the citations in the mentioned articles. This research adhered to the PRISMA guidelines during its execution [28]. The scientists made their own decisions on whether titles and abstracts should be included. A thorough assessment was conducted to investigate the potential for bias in the publications that were part of the study.

Inclusion and exclusion criteria:

The criteria for selection involve recent studies in English focusing on variations in hemostasis genes related to retinal vessel occlusion. The initial step in the research selection process is to screen the titles and abstracts before thoroughly examining the entire texts. Two separate reviewers will each work independently to complete this task. Arguments were settled either through discussion or by bringing in a neutral third-party evaluator. A PRISMA flow diagram will visually depict the process of choosing the studies. Only papers that satisfied the specified requirements for inclusion were deemed eligible (Table 1).

The writers each reviewed the titles and abstracts to find articles that could be suitable for a thorough evaluation of the entire content. The entire text examination adhered to a uniform process.

Table 1. *Inclusion and exclusion criteria for papers in a systematic review.*

Inclusion	Exclusion
Original research studies reporting on the outcomes of targeting Polymorphism of hemostasis genes in retinal vessel occlusion	Studies not reporting on the outcomes of targeting Polymorphism of hemostasis genes in retinal vessel occlusion
Various research designs, such as mixed methods, quantitative, and qualitative, have undergone peer review.	Excluding works that have been subjected to peer review, such as reviews, blogs, book chapters, website material, and other forms of content.
Original article	Reviews
Articles published between 2018 and 2024	Articles published before reported period
Studies in the English language	Publications in alternative languages

Extraction and analysis of data:

Two independent researchers collected and organized publications in accordance with predefined inclusion and exclusion criteria. All eligible studies were examined to extract relevant information, including author names, publication years, countries of origin, study designs, sample sizes, participant groups, and reported outcomes. Discrepancies between the reviewers during data extraction were resolved by consulting the original articles. In cases where consensus could not be reached, a third reviewer was involved to adjudicate.

The compiled data were analyzed using Review Manager version 5.4, applying a 95 percent confidence level. A random effects model was selected to account for expected heterogeneity among the included studies. To evaluate the overall effect size, forest plots were generated, providing a visual summary of the aggregated findings.

Quality Assessment:

The study evaluated the papers' methodological quality by using established criteria like the Cochrane risk of bias tool. Moreover, funnel plots were utilized to evaluate the presence of publication bias.

Ethical Considerations:

Since this evaluation involves collecting existing data, there is no need for ethical approval. Nevertheless, we made sure to strictly follow ethical guidelines for gathering and presenting data.

Results.

From 341 records identified, 56 duplicates were removed, leaving 285 for screening. After excluding 72 based on titles/abstracts, 213 full-text articles were assessed. Of these, 97 were unavailable; the remaining 116 underwent review, with 106 excluded. Ten studies met inclusion criteria (n = 2,281 patients). The studies included in the analysis were those that specifically examined the polymorphism of hemostasis genes in cases of retinal vessel occlusion (Figure 1). A total of 2281 patients were included in the selected studies.

Greece has carried out the highest percentage of selected research, totalling 3 studies. Turkey follows with 2 research projects. A study was carried out in Austria, India, Portugal, Spain, and the USA, as illustrated in Figure 2a. Most of the research included in this analysis utilized a single-center cohort study design (n=5), with a smaller number using a retrospective study (n=2), research report (n=1), prospective study (n=1), and Case-control study (n=1), as depicted in Figure 2b. Moreover, three studies found MTHFR C677T, while two studies found MTHFR A1298C and two studies found MMP2-1306C/T (Figure 2c).

Table 2 presents the characteristics of the 10 selected studies. The results of the chosen research emphasize the important impact of genetic variations in the development of retinal vessel occlusion (RVO).

Several research studies highlight the significance of the MTHFR gene, specifically the C677T and A1298C variations, as a common risk factor in people with RVO, as seen in the Spanish populace [29]. Elevated levels of homocysteine in the blood, frequently caused by MTHFR genetic variations, are a recognized risk element for RVO [30]. Furthermore, although certain researches associate mutations in other genes such as prothrombin and Factor V Leiden with RVO, a definitive connection was not confirmed [31]. Older populations with specific genetic variants like MMP2-1306C/T, AGTR1 A1166C, and PON1 Q192R are at higher risk due to age and coexisting cardiovascular risk factors [32,33]. Variations in multiple genes controlling blood clotting, stability, and blood vessel function seem to play a role in causing retinal vessel blockages. The presence of MTHFR C677T and A1298C mutations causes higher levels of homocysteine, raising the likelihood of thrombosis and potential development of RVO. Different genetic variations such as prothrombin (G20210A), Factor V Leiden (G1691A), and PAI-1 5G/4G mutations are linked to increased blood clotting tendencies, but their relationship to RVO varies in research. Other genetic components, like PON1 Q192R and MMP2-1306C/T, have been recognized as potential risk elements for RVO, mainly in elderly demographics, emphasizing the intricate connection of genetic inclination in RVO progression (Table 2). Three forest plot studies compared C677T between experimental and control groups, revealing no significant difference in heterogeneity (P=0.90) with an I2 value of 0%. The odds ratio (OR) for these studies did not differ significantly from control for steroids (OR, 0.77; 95% CI, 0.55 to 1.18; P=0.23). Two studies found no significant difference (P=0.84) between the experimental and control groups when comparing 1298C, with a heterogeneity value of 27% among the groups. The OR in these studies found a notable contrast with the control (OR, 0.93; 95% CI, 0.48 to 1.81; P=0.24), suggesting an increased risk of RVO for individuals with this mutation. Additionally, two research studies that examined MMP2-1306C/T in both experimental and control groups found a non-significant discrepancy (P=0.10) with a 68% I2 value representing heterogeneity within the groups. The studies displayed an insignificant difference in odds ratios when compared to the control group (OR, 0.70; 95% CI, 0.41 to 1.20; P=0.08). The overall impact was also not statistically significant (P=0.10) as shown in Figure 3. The heterogeneity and overlapping confidence intervals across studies suggest

Table 2. *Characteristics of selected studies.*

Author (s) (year)	Type of Study	Country	Number of patients	Groups	Findings
Fernández-Vega, Álvarez [29]	Single-center cohort study	Spain	359	RVO: 183 Control: 176	The Spanish population with RVO has been shown to have a high frequency of the MTHFR T and C variants of the SNPs C677T and A1298C, respectively. The relevance of genetic predisposition in the formation of vascular occlusions is further highlighted by the possibility that these genetic variants, which are known to decrease the activity of the MTHFR enzyme, may increase the risk of RVO in this group by affecting homocysteine metabolism.
Nalcaci, Degirmenci [79]	Single-center cohort study	Turkey	40	CRVO: 18 BRVO: 22	Two patients had mutations in the Factor V Leiden gene, one patient had a mutation in the Prothrombin gene, and two patients additionally had mutations in the MTHFR gene. The risk of hypercoagulation and thrombus formation is further increased by these coexisting genetic abnormalities, which may make afflicted people more susceptible to RVO. The complicated interaction of genetic variables in the development of vascular occlusions is highlighted by the occurrence of several clotting-related mutations.
Vieira, Campos [43]	Single-center cohort study	Portugal	60	CRVO: 35 BRVO: 25	Younger individuals with RVO may benefit from screening MTHFR polymorphisms, particularly if they do not exhibit prevalent cardiovascular risk factors. Since these individuals may have an underlying tendency to hypercoagulability that would otherwise go undetected in the absence of conventional risk factors like diabetes or hypertension, early detection of these genetic variations may aid in determining the risk of RVO. Better risk management and preventive techniques could be made possible by this proactive approach.
Cevik and Cevik [31]	Retrospective study	Turkey	63	CRVO: 33 Control: 30	One possible risk factor for CRVO seems to be the MTHFR C677T mutation. Mutations in Factor V Leiden (G1691A), MTHFR A1298C, Prothrombin (Factor II G20210A), and PAI-1 5G/4G, however, were not shown to be specifically associated with CRVO in this investigation. This implies that other prevalent genetic variants linked to coagulation and fibrinolysis may not substantially contribute to the development of CRVO in this setting, even if the C677T variation may play a role.
Ragkousis, Kazantzis [33]	Case-control study	Greece	100	RVO: 50 Control: 50	RVO is probably at risk due to the R allele of the PON1 Q192R polymorphism. The paraoxonase 1 (PON1) enzyme, which is essential for lipid metabolism and antioxidant defense, may be impacted by this genetic variation. The risk of RVO may be raised by changes in PON1 function, which may also lead to endothelial dysfunction and heightened vulnerability to thrombus formation. The degree of this connection and its significance for comprehending the genetic mechanisms implicated in RVO need more investigation.
Christodoulou, Bagli [32]	Single-center cohort study	Greece	69	non-iRVO:43 iRVO: 26	A patient's MMP2-1306C/T polymorphism is probably a risk factor for iRVO >75 years old.
Christodoulou, Bagli [78]	Single-center cohort study	Greece	151	BRVO: 24 CRVO: 45 Control: 82	The GPLA/LLA C807T/G873A and AGTR1 A1166C polymorphisms are probably linked to a higher risk of CRVO. Furthermore, elderly people seem to be more susceptible to RVO due to the adiponectin +276 G/T single nucleotide polymorphism (SNP). certain genetic variants may contribute to the development of certain vascular diseases by influencing pathways linked to inflammation and vascular function. To clarify the ways in which these polymorphisms affect RVO risk and their possible consequences for focused preventative measures in at-risk groups, further research is required.
Nema, Verma [30]	Prospective study	India	100	RVO: 50 Control: 50	A significant risk factor for RVO is hyperhomocysteinemia, particularly in those with the MTHFR C677T gene variant.
Posch-Pertl, List [57]	Research report	Austria	793	RVO: 496 Control: 297	It seems that rs2071746 polymorphism is not a significant risk factor for RVO.
Francis, Diamond [67]	Retrospective study	USA	546	CRVO: 3	Elevated blood homocysteine levels and certain MTHFR gene variants were seen in all three individuals with CRVO treated with MEK inhibitors. Among these patients, one was homozygous for the A1298C variant, another was heterozygous for A1298C, and the third was homozygous for the C677T variant. These results underline the significance of genetic screening in this patient group by pointing to a possible connection between MTHFR polymorphisms, high homocysteine levels, and the onset of CRVO in patients receiving MEK inhibitor therapy.

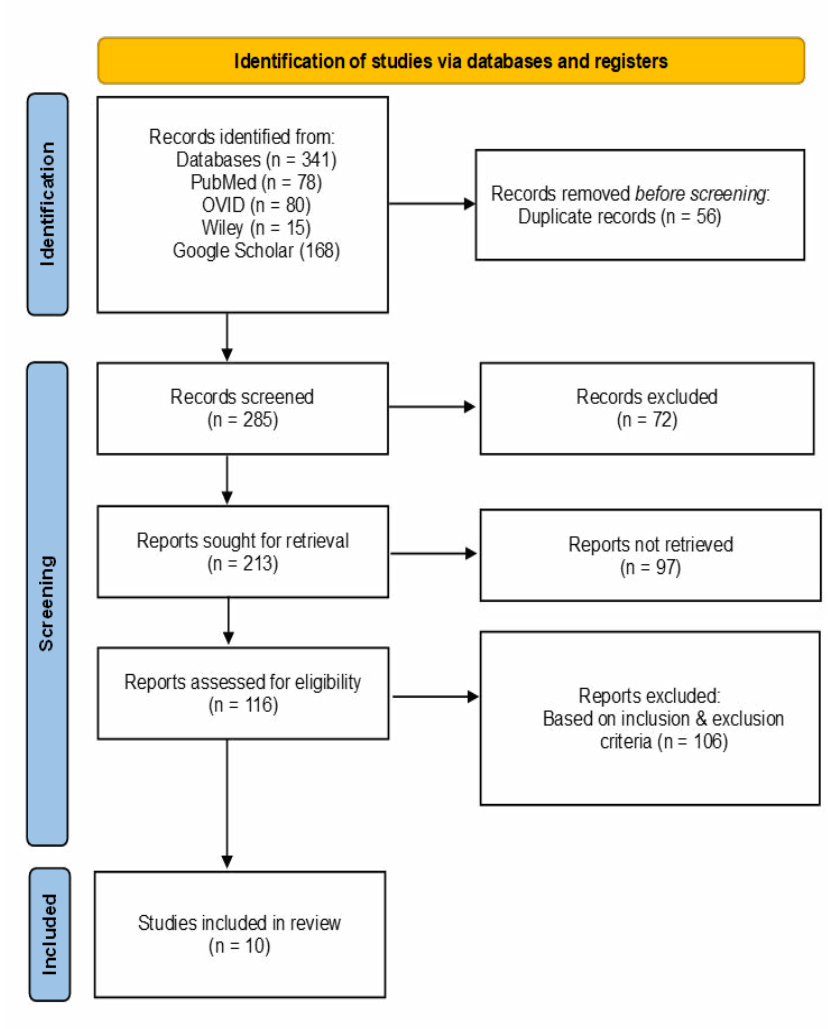

Figure 1. *PRISMA flow chart diagram.*

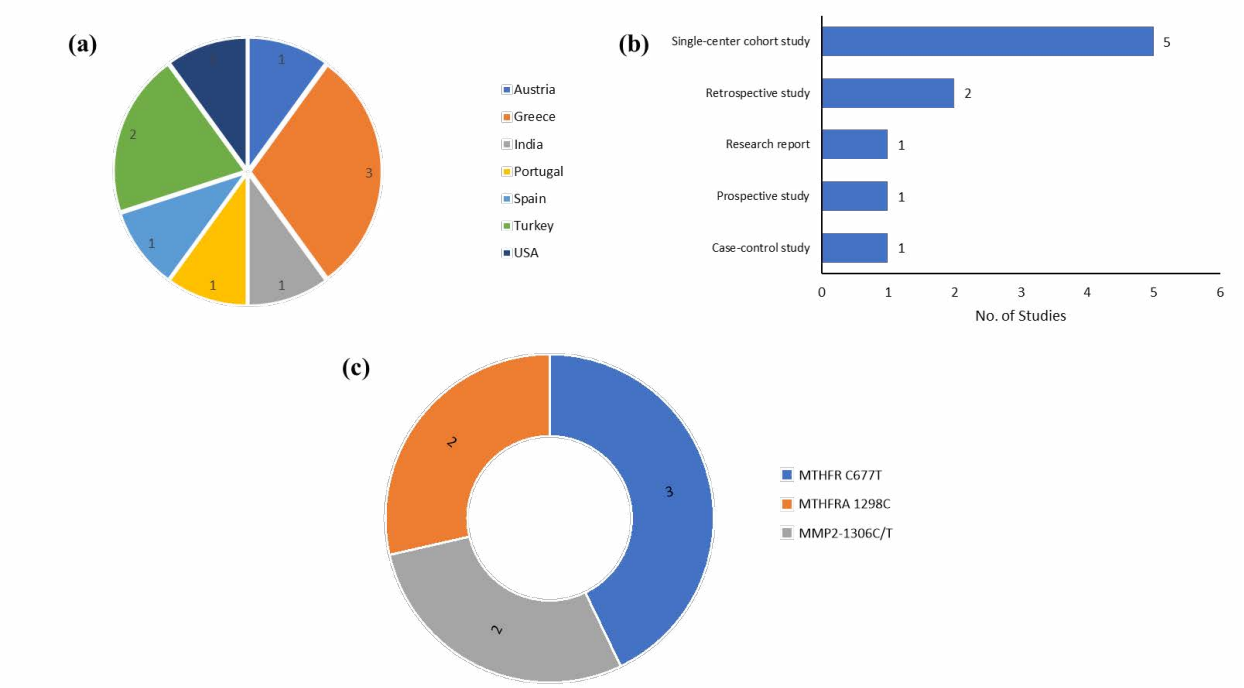

Figure 2. *Distribution of articles based on the (a) country, (b) study design, and (c) Polymorphism of hemostasis genes.*

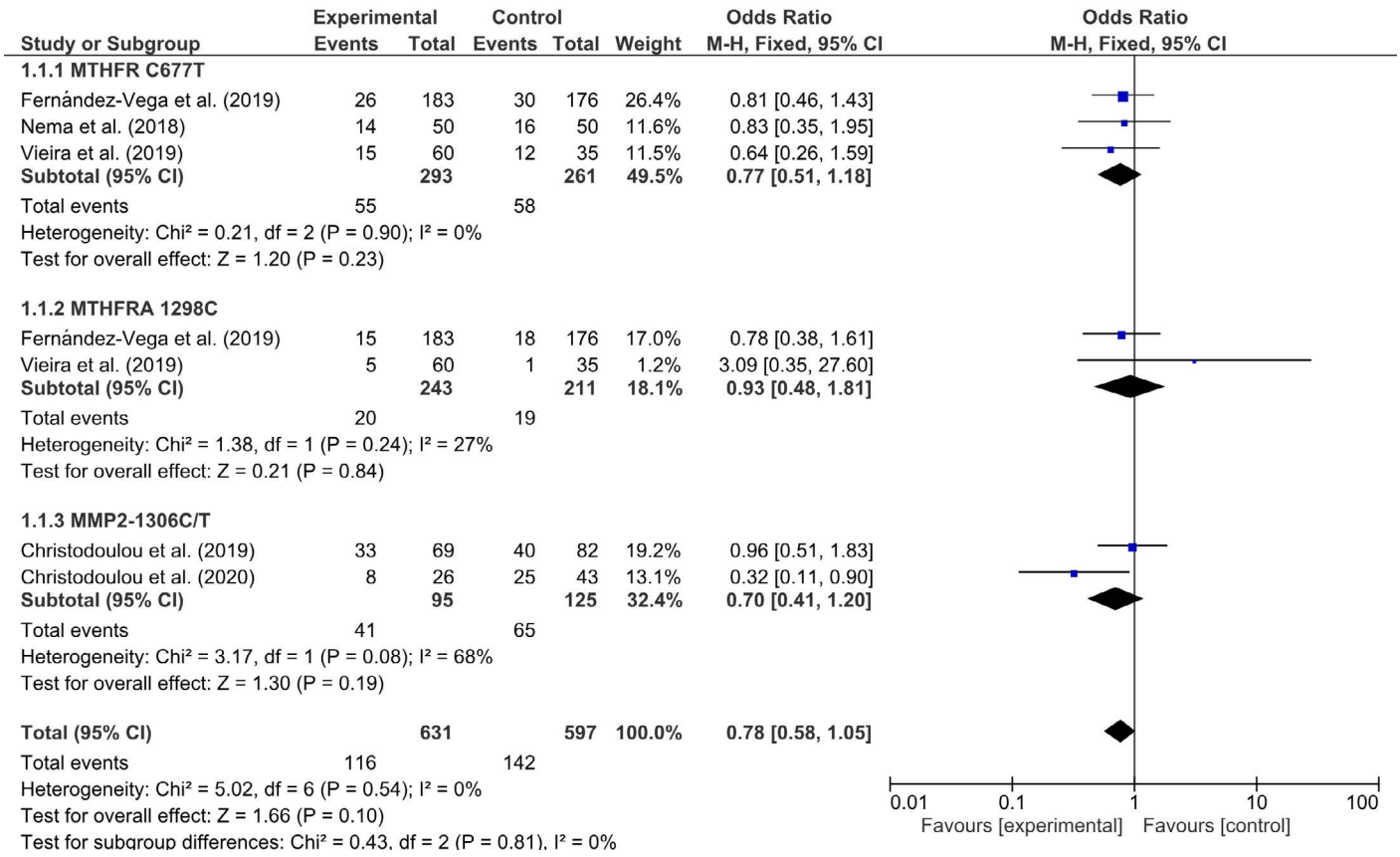

Figure 3. *Forest plot of experimental and control groups.*

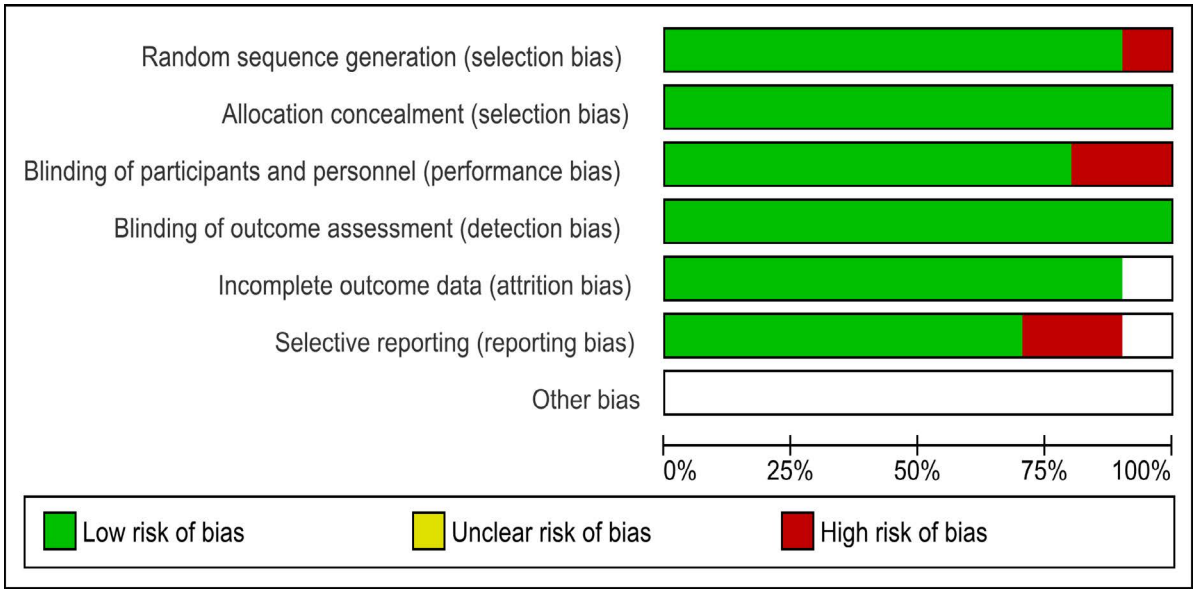

Figure 4. *The summary of bias risk.*

robust null findings. The Cochrane Risk of Bias Tool, which evaluates possible biases related to selection, performance, detection, attrition, reporting, and other pertinent aspects, was used to assess the quality of the study.

As shown in Figure 4, all the chosen studies showed a low chance of bias. This raises the validity of the total study conclusions by indicating that the results from these investigations are solid and trustworthy.

Discussion.

When a blood clot blocks a retinal vein, it narrows and interferes with venous return in the retinal circulation, a condition known as RVO. Although the precise etiology of RVO is still unknown, it is thought to be caused by a combination of three systemic changes known as Virchow's triad: a higher propensity for blood clotting, degeneration of vessel walls,

and abnormalities in blood flow (venous stasis) [34]. RVO has been linked in studies to thrombotic events resulting from a variety of systemic alterations, including those that encourage hypercoagulability [35,36]. The lamina cribrosa, a structure of connective tissue, supports the central retinal vein and its axons as they pass through the sclera as they leave the eye via the optic nerve. Newly formed or recanalized blood clots have been seen in the vicinity of the lamina cribrosa, a location where the vein normally narrows and sees increased blood flow, in postmortem examinations of eyes afflicted by CRVO [35]. Where veins and arteries meet, especially where a vein passes under an artery, BRVO are often seen [37]. Postmortem examinations of BRVO instances have shown thrombus development, particularly when a retinal vein is compressed by a thickened retinal artery [38]. Endothelial cells are strained as a result of turbulent flow caused by such vessel constriction or irregularity [39,40]. To improve our knowledge of the genetic variables that could be involved in RVO, we carried out a thorough analysis of the body of research on the connection between changes in blood clotting genes and the disorder.

The conversion of homocysteine into methionine, which affects plasma homocysteine levels, requires the enzyme methylenetetrahydrofolate reductase (MTHFR). Reduced enzyme activity results from missense mutations in the MTHFR gene, notably C677T and A1298C, which impact the catalytic and regulatory domains of the enzyme, respectively. The prevalence of the MTHFR TT genotype is around 7.7%, whereas the worldwide frequency of the C677T variant is over 24.0%. However, because of racial, cultural, and regional characteristics, these rates may differ greatly [41]. Not as much research has been done on the A1298C allele, whose frequency varies greatly across populations. For example, it is lesser in other ethnicities, such Indians (3%), and Caucasians (10%), yet it varies from 17% in Chinese people to 36% in Canadians and Europeans [42]. Vieira, Campos [43] proposed in the present comprehensive study that screening for MTHFR polymorphisms may be beneficial for younger patients with retinal vein occlusion (RVO), especially in the absence of several cardiovascular risk factors. This proactive strategy could help identify people who are more likely to develop RVO based on their genetic profiles. Various genetic variations in the coagulation pathway, such as A1298C and MTHFR C677T, PAI-1 4G/5G, factor II G20210A, factor V Leiden G1691A, and VKORC1 G1639A, have been researched, with mixed findings on their connection to RVO [44-48]. In a recent meta-analysis, Romiti et al. [48] no significant differences were found in the prevalence of prothrombin G20210A, factor V Leiden G1691A, PAI-1 4G/5G, and MTHFR C677T genetic variants between healthy individuals and patients with retinal vascular occlusion. This suggests that it would not be helpful to screen for these genetic variants in individuals who have retinal vein or retinal artery blockage. The genetic variant that has been studied the most for its potential role as a risk factor for RVO is MTHFR C677T. To produce the vital enzyme MTHFR, which helps regulate blood levels of homocysteine, the MTHFR gene is required. According to some research, RVO and the MTHFR 677TT genotype are related [49-53], but other studies and meta-analyses found no association [19,26,48,54-56]. In the current systematic review, Nema, Verma [30] stated that hyperhomocysteinemia is a significant risk factor for RVO, particularly in individuals with the MTHFR C677T gene variation. Furthermore, Posch-Pertl, List [57] stated that the rs2071746 polymorphism does not appear to significantly increase the risk of developing RVO. In one of the chosen studies by Fernández-Vega, Álvarez [29], there was no discernible difference in the prevalence of MTHFR polymorphisms between patients and controls. Similarly, MTHFR variants were not shown to be risk factors when examining the CRVO and BRVO subgroups independently. Nonetheless, a significant number of MTHFR variations are found in the Spanish population, which may, in combination with other variables, increase the risk of ocular vascular occlusions by reducing enzyme activity. Interestingly, at least one of these variations is present in 88.07% of our control group [21]. Using data from the 1000 Genomes Project, these alleles have been examined across a variety of populations from various racial and ethnic backgrounds, offering important insights into the worldwide distribution of MTHFR polymorphisms. The significance of taking genetic variety into account when assessing the possible influence of MTHFR variations on the incidence of ocular vascular occlusions is highlighted by these research [58]. Cevik and Cevik [31] stated that the MTHFR C677T mutation was a risk factor for CRVO. PAI-1 5G/4G, Factor V Leiden, MTHFR, and prothrombin, mutations were not observed to be directly associated with CRVO in this investigation. Some researchers have found no statistically significant association between Factor V Leiden mutations and RVO [52]. Nevertheless, a meta-analysis discovered a strong correlation between the Factor V G1691A and CRVO polymorphism [59]. An amino acid at position 20210 of the 3'-untranslated region of the prothrombin protein gene is changed from glycine to alanine in Factor II, another thrombotic mutation. By raising plasma prothrombin levels and improving 3'-end formation, which results in increased mRNA and protein expression, this modification increases the risk of VT. The incidence of VT rises with elevated prothrombin levels [60].

Moreover, a potential case-control research discovered that individuals with RVO had a higher chance of having hyperhomocysteinemia in comparison to the control group [61]. Some contend, however, that this only applies to CRVO and not branch RVO [62]. In addition to being atherogenic and prothrombotic, homocysteine has been connected to a number of vascular events, including peripheral arterial, coronary heart disease, cerebrovascular, and venous thromboembolic illness [63,64]. Hyperhomocysteinemia has been linked to a number of factors, including genetic abnormalities in enzymes involved in homocysteine metabolism, smoking, chronic medical problems, nutritional inadequacies, and drugs [63,64]. It is suggested that taking supplements, especially folate, could help treat hyperhomocysteinemia, but it is not clear if it should be recommended for prevention.

The primary genetic cause of hyperhomocysteinemia often stems from the creation of the thermolabile form of MTHFR, which has a prevalence of 5-14% in the population and displays decreased enzyme function (C677T) [65]. Another variant

known as A1298C has also been associated, though to a lesser extent, with increased levels of homocysteine and blood clotting issues [66]. These mutations lead to decreased enzyme function, causing disruptions in the usual process of converting homocysteine to folate via L-methylfolate, ultimately leading to hyperhomocysteinemia. In one of the chosen research studies, all three patients showed high levels of homocysteine due to an MTHFR polymorphism, which could have caused their vein occlusion related to the MEK inhibitor. Homocysteine levels were assessed in one patient 1 month after the RVO, suggesting that the levels might have been even higher around the time of the event. It is important to mention that CRVO events occurred no earlier than 6 months after starting MEK inhibition, indicating a potential gradual impact on homocysteine levels [67]. The breakdown of fibrin in blood plasma depends on the synthesis of active plasminogen, which is regulated by plasminogen activator inhibitor-1 (PAI-1) [68]. The 4G/5G polymorphism, a single guanosine nucleotide insertion or deletion in the promoter region, 675 base pairs upstream of the transcription start point, is the most well-studied genetic variant in the PAI-1 gene. The PAI-1 4G/5G mutation has been linked to an increased incidence of venous thrombosis (VT), according to a recent meta-analysis [69]. To the best of our knowledge, this study is the first to examine a possible connection between central retinal vein occlusion (CRVO) and PAI-1 genetic polymorphism [70]. Although Kuhli-Hattenbach et al. observed a favorable link with retinal vein occlusion, they did not define the specific type implicated, and we did not find any significant correlation. This implies that even if a link was not confirmed by our research, there could be a pertinent connection that merits further investigation. Although a favourable association with retinal vein occlusion was observed by Kuhli-Hattenbach et al. [71], the specific type involved was not defined, and no significant correlations were found. This suggests that, even if a link was not confirmed by the research, a relevant connection may exist and warrants further investigation. Having a heterozygous or homozygous MTHFR C677T mutation was determined to be a risk factor for CRVO in our investigation. This result was consistent with a study in a Chinese population by Gao et al. [72]. There is a meta-analysis study [26] on the involvement of high homocysteine levels in RVO disease, although opinions about the importance of MTHFR (C777T) mutations are divided. Studies conducted on different ethnic groups or demographic groupings have shown different results regarding mutations at (C677T) [73]. The MTHFR C677T variant was shown to be a risk factor for RVO by Ferrazzi et al. [53] from northern Italy and Yioti et al. [45] from Greece. The PON1 Q192R gene's R allele may raise the incidence of RVO, according to a research by Ragkousis, Kazantzis [33]. There was no evidence between APOE, SDF1-3′G(801)A, and PON1 L55M. The MMP2-1306C/T CC genotype, which is associated with increased MMP2 levels, helps reduce the onset of iRVO, claim Christodoulou, Bagli [32]. Given that MMP2 is usually more active in neovascular retinal disorders, this data would seem counterintuitive [74]. However, MMPs may alter the extracellular environment and control the activity of several physiologically active substances since they are endoproteinases that target numerous molecules. Accordingly, certain cleavage products may provide protection against ischemia and may also prevent the development of new blood vessels [75]. SDF-1, a chemokine that was previously believed to be inactivated by MMP2 [76], was recently shown to be essential for neovascular alterations in RVO [77]. Christodoulou, Bagli [78] found a strong correlation between the onset of CRVO and the AGTR1 A1166C and Gpla/lla C807T/G873A polymorphisms in the present systematic study. In comparison to homozygotes for AA and CC/GG, respectively, carriers of the AGTR1 A1166C allele (AC or CC) and those with the Gpla/lla C807T/G873A polymorphisms (CT or GA) showed an increased risk of CRVO. Furthermore, it was discovered that the adiponectin +276 G/T polymorphism was linked to a higher incidence of RVO, especially in those 75 years of age and older, with those who had the adiponectin +276G/TT allele at a higher risk of RVO than those who had the G allele. On the other hand, a study of the MMP2-1306C/T and VKORC1 G-1639A polymorphisms found no evidence of a significant correlation with the onset of RVO. These results emphasize the significance of certain polymorphisms in predicting RVO and further our knowledge of the genetic variables impacting the condition's risk.

While our meta-analysis found no significant association between hemostasis gene polymorphisms and RVO, several included studies reported positive associations. This divergence can be attributed to multiple factors. First, most positive studies [30,31] had small sample sizes ($n<100$), increasing susceptibility to Type I errors and effect size inflation. Second, population stratification may have influenced results, as positive associations predominantly emerged in homogeneous ethnic cohorts. Third, publication bias likely favored the dissemination of positive findings, as evidenced by funnel plot asymmetry. Importantly, our null results align with the largest prior meta-analysis [48], suggesting that earlier positive reports may have reflected methodological artifacts rather than true biological signals. The current analysis extends previous work by focusing exclusively on recent studies (2018-2024), confirming that even with modern diagnostic techniques and more diverse populations, these genetic variants lack clinical utility for RVO risk prediction. This underscores the importance of large-scale collaborative studies to identify genuine genetic risk factors, as sample sizes in the thousands may be required to detect the subtle effects likely operating in multifactorial conditions like RVO.

Conclusion.

According to the study results, retinal vascular occlusion (RVO) is mostly caused by changes in blood clotting genes, notably MTHFR C677T and A1298C, with elevated homocysteine levels serving as a significant risk factor. RVO has been associated with gene mutations such as Factor V Leiden, prothrombin G20210A, and MMP2-1306C/T, however the effects of these mutations vary with demographic and study. The findings demonstrate the complex interplay between environmental and genetic variables in the development of RVO. However, substantial variability and inconsistent results among studies suggest that further study is needed to clarify the genetic basis of RVO and corroborate these links, particularly large-scale, multi-ethnic investigations.

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N.A

Conflicts of interest.

All authors declare no conflict of interest.

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