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Review Article

Advancements and controversies in vascular malformation management: A Systematic review.

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Abstract

Background
Congenital vascular malformations encompass a wide spectrum of anomalies, ranging from isolated capillary, venous, lymphatic, and arteriovenous malformations to complex mixed forms. These anomalies may occur as solitary lesions with minimal impact or as part of syndromic conditions, such as Klippel-Trenaunay Syndrome and Parkes-Weber Syndrome, which are associated with significant morbidity due to limb overgrowth and tissue abnormalities. Additionally, the PIK3CA-related overgrowth spectrum (PROS) represents a distinct subset driven by somatic PIK3CA mutations, which complicates diagnosis and management.
Objective: This study aims to systematically review the classification, pathogenesis, genetic factors, diagnostic approaches, and treatment modalities for vascular malformations and associated syndromes.

Methods
In order to perform a systematic review, peer-reviewed publications, clinical recommendations, and expert consensus statements on vascular malformations were found using PubMed, Scopus, Web of Science, and Google Scholar. Studies published within the last two decades were prioritized, with an emphasis on recent advancements.

Results
Genetic insights have redefined vascular malformation classification, with PIK3CA, TEK (TIE2), and RASA1 mutations playing a crucial role in pathogenesis. Advanced imaging techniques, including MRI and digital subtraction angiography (DSA), remain the gold standard for precise diagnosis, while genetic testing enhances diagnostic accuracy and guides personalized treatment. Conventional therapies such as sclerotherapy and embolization demonstrate 70–85% success rates; however, targeted molecular therapies, including Sirolimus and Alpelisib, have shown superior outcomes in PIK3CA-related cases.

Conclusion
The evolving landscape of vascular malformation management highlights the shift toward precision medicine, integrating advanced imaging, genetic diagnostics, and molecular-targeted therapies.

Recommendations
Encouraging international collaborations among researchers, clinicians, and geneticists can accelerate advancements in vascular malformation research. Quality-of-life assessments should be incorporated into research to evaluate the long-term psychological and functional impacts of various treatments.

Keywords: *Malformations, PIK3Ca mutation, Vascular overgrowth, Sclerotherapy, Embolization*
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Introduction

Vascular malformations are a diverse group of congenital anomalies affecting blood and lymphatic vessels, ranging from isolated capillary and venous malformations to

complex mixed lesions involving multiple vascular components. While some malformations remain asymptomatic, others lead to significant morbidity, including pain, functional impairment, and life-threatening complications [1-5]. These conditions may occur independently or as part of syndromic disorders such as Klippel-Trenaunay syndrome and Parkes-Weber syndrome, both of which involve vascular anomalies combined with limb overgrowth and tissue hypertrophy [6,7].

Recent advances in molecular biology have uncovered key genetic mutations underlying these disorders, particularly in genes such as *PIK3CA, TEK,* and *RASA1*, which play crucial roles in vascular development and signaling pathways [8,9]. Understanding these genetic mechanisms has paved the way for targeted therapies, such as sirolimus and alpelisib, offering new treatment options for patients with previously untreatable vascular anomalies [10].

Although vascular malformations are congenital, their clinical manifestations vary over time. Low-flow malformations are often identified in childhood, whereas high-flow lesions may remain asymptomatic until adolescence. The management of these conditions requires a long-term, multidisciplinary approach, particularly in pediatric patients, due to their progressive nature and potential impact on growth and development [11-13]. Sclerotherapy is typically the first-line treatment for venous malformations (VMs), aiming to reduce lesion volume and alleviate symptoms while minimizing surgical risks [14,15]. Depending on the nature of the lesion and the skill of the physician, different sclerosing drugs are utilized, including ethanol, doxycycline, bleomycin, and sodium tetradecyl sulfate (STS) [14]. Imaging plays a critical role in guiding treatment, evaluating lesion size, vascular supply, and potential risks associated with embolization and sclerotherapy [14].

Surgical resection remains an option for select cases, particularly for well-defined VMs or arteriovenous malformations (AVMs). Preoperative embolization with n-butyl cyanoacrylate (n-BCA) glue can reduce the extent of malformation and recurrence risk [14,15]. Moreover, multimodal approaches, such as combining sclerotherapy with stereotactic radiosurgery (SRS), have demonstrated improved outcomes in AVM management [16]. However, embolization-only strategies have been linked to increased recurrence due to angiogenesis triggered by hypoxia [16].

Classification of vascular malformations has evolved to enhance diagnostic accuracy and treatment planning. Simple vascular malformations, combined vascular malformations, malformations associated with other anomalies, and malformations involving major vessels are the four groups into which the 2018 update to the International Society for the Study of Vascular Anomalies (ISSVA) classification divides anomalies to standardize nomenclature [17-20]. The Hamburg classification system, originally developed in 1988, categorizes anomalies based on embryologic development, distinguishing "truncular" lesions with significant hemodynamic effects from "extratruncular" lesions with growth potential [21].

Venous, lymphatic, and arteriovenous malformations exhibit distinct clinical and pathological features. VMs, the most common type, affect 1% to 4% of the population and are characterized by soft, compressible, bluish lesions that vary in size based on position and hormonal changes [22,23]. Lymphatic malformations (LMs) are categorized as macrocystic, microcystic, or mixed and can fluctuate in size due to infection, bleeding, or inflammation [22]. AVMs, composed of a direct artery-to-vein shunt without an intervening capillary network, typically become symptomatic during adolescence and may enlarge in response to puberty or trauma [24,25].

Aesthetic and functional concerns significantly impact treatment decisions. While cosmetic improvement is a consideration, interventions should be guided by the patient's self-perception rather than parental preference, particularly in pediatric cases [13]. Children with extensive vascular malformations often require multiple interventions, necessitating clear communication about the chronic nature of their condition. A multidisciplinary team—including dermatologists, pediatricians, genetic specialists, plastic and orthopedic surgeons, interventional radiologists, and allied health professionals—plays a crucial role in optimizing outcomes and addressing both medical and psychosocial challenges [13].

Despite advancements in classification and treatment, challenges persist regarding optimal management strategies, long-term outcomes, and consensus on best practices. Many cases remain misdiagnosed or undertreated due to the complexity of these conditions [26-29]. Examining current developments, continuing discussions, and growing consensus in the diagnosis and treatment of vascular malformations is the goal of this comprehensive review. This review aims to provide a thorough overview of the changing landscape of vascular malformation treatment by combining the most recent evidence.

Objectives

Current information on the many symptoms, underlying mechanisms, genetic variables, and treatment modalities of vascular malformations and related syndromes is to be synthesized in this systematic review.

By critically evaluating recent advancements, identifying persistent clinical and molecular challenges, and assessing expert consensus, this study seeks to:

Enhance understanding of the classification, diagnosis, and treatment of vascular malformations.

Compare existing treatment modalities, including surgical, sclerotherapy, and embolization techniques, in terms of efficacy, safety, and recurrence risk.

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Highlight key debates and emerging consensus in vascular malformation management.
Encourage multidisciplinary collaboration to improve diagnostic precision, therapeutic strategies, and overall patient care.

Materials and methods

To guarantee a methodical and open approach, this systematic review was carried out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.

Search strategy and selection

A comprehensive literature search was performed across multiple databases, including PubMed (last searched 10 April, 2025), Scopus (last searched 12 April, 2025), Web of Science (last searched 10 April, 2025), and Google Scholar (last searched 15 April, 2025), to identify relevant peer-reviewed articles, clinical guidelines, and expert consensus reports. The search included studies published within the last two decades, with priority given to advancements from the past five years.
The following keywords and Medical Subject Headings (MeSH) were included in the search strategy:
"Vascular malformations" OR "congenital vascular anomalies"
"Arteriovenous malformations (AVMs)" OR "venous malformations (VMs)"
"Sclerotherapy" OR "embolization" OR "surgical management"
"Genetic factors in vascular malformations" (e.g., *PIK3CA, TEK, RASA1*)
"Targeted therapy for vascular malformations" OR "molecular treatment"

Inclusion criteria

- Peer-reviewed original research, systematic reviews, meta-analyses, and expert consensus reports.
- Publications discussing vascular malformation classification, pathophysiology, genetic factors, diagnostic approaches, and treatment options.
- Research highlighting novel therapeutic approaches, including targeted molecular therapies and interventional procedures.
- Studies that address controversies and differing viewpoints in vascular malformation management.

Exclusion criteria

- Non-English studies without accessible translations.
- Case reports with limited clinical applicability.
- Studies lacking substantial clinical or experimental evidence.

Selection process

Two reviewers independently screened the titles and abstracts of all retrieved articles for relevance. Full-text articles were then assessed independently by the same reviewers to determine eligibility based on the inclusion and exclusion criteria. Disagreements were resolved through discussion or consultation with a third reviewer when necessary.

Bias

The studies included in this review may not comprehensively represent all research on vascular malformations, as the selection process may have favored studies with positive findings or those published in high-impact journals. The review incorporates studies with different methodologies, sample sizes, and follow-up durations, which may lead to variability in reported outcomes and limit direct comparisons.

Data collection and analysis

Data extraction

Key information extracted included study design, patient population, genetic findings, clinical outcomes, and the effectiveness of different treatment approaches. Data extraction was done using keywords such as malformations, PIK3Ca mutation, and vascular overgrowth. Other than prevalence and clinical syndromes were assessed. Advantages and utility modality were also assessed.

Expert recommendations

The review incorporated guidelines from the International Society for the Study of Vascular Anomalies (ISSVA) and other prominent organizations.
By adopting this structured approach, this review provides a comprehensive synthesis of vascular malformation research, emphasizing key advancements, ongoing challenges, and emerging expert consensus.

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Table 1. Treatment strategies for vascular malformations

Surgical Management of AVMs and Other Vascular Lesions	Sclerotherapy in the Management of AVMs and Other Vascular Lesions	Embolization in the Management of AVMs and Other Vascular Lesions
Surgery can be a safe and efficient therapeutic option for vascular anomalies of the upper extremities, even if non-surgical treatment is often preferred. The literature displays a range of complication rates for non-surgical treatment of vascular anomalies in the upper extremities. A variety of complication rates are seen in studies on non-surgical therapy of vascular abnormalities in the upper extremities [14, 15, 16].	When a sclerosing agent was used as part of a sclerotherapy treatment, the lesion completely disappeared without any collateral anastomosis. The noninvasive, nontraditional method used to treat VM patients has several advantages, such as a more aesthetically pleasing result, a lower risk of blood loss and transfusion risk, and cost-effectiveness because the patient can receive treatment as an outpatient [14, 15].	Embolization is used to treat AVM; they are not a treatment for it. They reduce the AVM's size and alleviate symptoms. The AVM is expected to re-expand over time. Throughout their lives, the majority of patients receive this treatment multiple times. Reducing the symptoms to a minimum is the aim [15, 16].

Results

Figure 1 represents the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram of the literature search and selection.

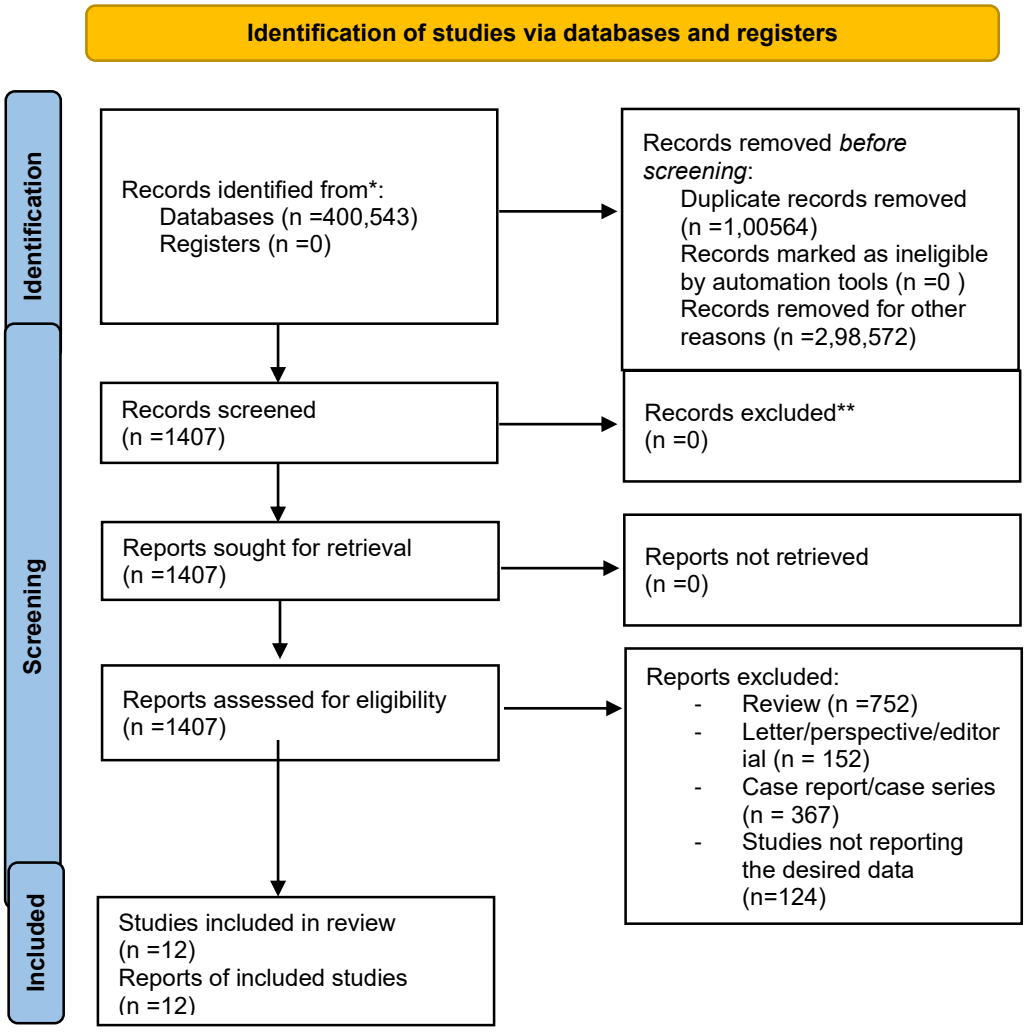

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Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow diagram of the literature search and selection

Risk of bias assessment

Several studies met the inclusion criteria and were included in this review [6, 7, 8, 9, 10, 11, 12, 13, 27, 28, 29, 30]. Table 2 represents the Risk of Bias assessment that has been done using the Newcastle-Ottawa Scale (NOS). With its design, substance, and user-friendliness focused on the objective of integrating the quality assessments in the interpretation of meta-analytic data, it was utilized to evaluate the caliber of non-randomized investigations.

The NOS is a widely used tool for assessing the quality and risk of bias in observational studies, including cohort and case-control studies. It evaluates three main domains: selection, comparability, and outcome. Higher scores indicate a decreased probability of bias. A study's overall score goes from 0 to 9. According to the NOS, studies with ratings of 0–3, 4–6, and 7–9 are classified as having high, moderate, or low risk of bias, respectively. The NOS also offers recommendations on how to interpret the scores. Depending on the degree of bias risk, a set of criteria is used to evaluate each domain, and each criterion is given a score of 0, 1, or 2.

Table 2. Risk of bias assessment using the Newcastle-Ottawa Scale (NOS)

Study	Selection	Comparability	Outcome	Summary
Luks VL et al, 2017	4	2	3	8
Vahidnezhad H et al, 2018	4	2	3	8
Limaye N et al, 2015	4	2	2	9
Castillo SD et al, 2016	4	2	2	9
Lapinski PE et al, 2017	4	2	3	9
Soblet J et al, 2017	4	2	2	8
Boscolo E et al, 2021	4	2	3	8
Smolak L et al, 2011	4	2	2	9
Mulliken JB et al, 1982	4	2	3	8
Wassef M et al, 2015	4	2	2	9
Greene AK et al, 2011	4	2	2	8
Mazereeuw-Hautier J et al, 2022	4	2	2	8

This review analyzed various aspects of vascular malformations, including classification, pathogenesis, genetic factors, diagnostic approaches, and treatment advancements. The findings are summarized in different sections below, supported by tabulated data for clarity.

Low-flow (capillary, venous, lymphatic) and high-flow (arteriovenous) lesions are the two main categories into which vascular malformations fall. There are also mixed types, including capillary-lymphatic-venous malformations (CLVM). Because of the concomitant limb overgrowth and tissue abnormalities, syndromic vascular malformations, such as Klippel-Trenaunay Syndrome (KTS) and Parkes-Weber Syndrome (PWS), present with more complicated symptoms

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Table 3: Classification and prevalence of vascular malformations

Type of Malformation	Flow type	Prevalence (%)	Common Syndromes
Capillary Malformation (CM)	Low-flow	0.3-0.5	Sturge-Weber syndrome [27]
Venous Malformation (VM)	Low-flow	1.0	Blue Rubber Bleb Nevus Syndrome [27-30]
Lymphatic Malformation (LM)	Low-flow	0.2	CLOVES Syndrome [27-30]
Arteriovenous Malformation (AVM)	High-flow	0.1	Parkes Weber Syndrome [27-30]
Capillary-Lymphatic-Venous Malformation (CLVM)	Mixed	Rare	Klippel-Trenaunay Syndrome [27-30]

Genetic mutations play a critical role in vascular malformation development. The PIK3CA gene mutation is commonly associated with overgrowth syndromes, while RASA1 mutations are linked to arteriovenous malformations. Identifying these mutations has led to

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potential targeted therapies, such as PI3K inhibitors for PROS-related vascular anomalies.

Table 4: Genetic insights and molecular pathogenesis

Gene Mutation	Associated Malformation	Pathogenic Mechanism
PIK3CA	Capillary, venous, and lymphatic malformations	Activates PI3K/AKT/mTOR pathway, causing vascular overgrowth [7-12]
RASA1	Arteriovenous malformations	Dysregulates RAS/MAPK signaling, leading to abnormal vessel formation [7-12]
TEK (TIE2)	Venous malformations	Impairs endothelial cell function and vessel stability [7-12]
GNAQ	Sturge-Weber Syndrome	Causes abnormal vascular proliferation in the brain and skin [7-12]

Early diagnosis is crucial for managing vascular malformations effectively. Advanced imaging techniques, such as Doppler ultrasound, MRI, and digital subtraction angiography (DSA), help differentiate between various malformation types.

Table 5: Diagnostic approaches and imaging techniques

Diagnostic Modality	Utility	Advantages
Doppler Ultrasound	Initial assessment of blood flow dynamics	Non-invasive, cost-effective [12,13]
Magnetic Resonance Imaging (MRI)	Differentiates low-flow vs. high-flow lesions	High-resolution soft tissue contrast [12,13]
Digital Subtraction Angiography (DSA)	Gold standard for AVMs	Provides detailed vascular anatomy for intervention planning [12,13]
Genetic Testing	Identifies mutations in complex syndromes	Facilitates personalized therapy [12,13]

Management of vascular malformations varies based on type and severity. Standard approaches include sclerotherapy, embolization, and surgical excision, while novel therapies such as targeted molecular inhibitors are being explored.

Table 6: Treatment strategies and emerging therapies

Treatment Modality	Indications	Effectiveness
Sclerotherapy	Venous and lymphatic malformations	High success in symptom relief [6-9]
Embolization	Arteriovenous malformations	Reduces blood flow, preventing rupture [6-9]
Surgical Resection	Large or symptomatic malformations	Definitive removal but risk of recurrence [6-9]
Sirolimus (mTOR Inhibitor)	PIK3CA-related overgrowth syndromes	Promising results in reducing lesion size [6-9]

Discussion

According to their hemodynamic characteristics, vascular malformations have traditionally been divided into low-flow lesions (venous malformations, lymphatic malformations, capillary malformations) and high-flow lesions. By combining genetic and molecular insights, the ISSVA categorization has improved this method and produced a more accurate framework. Recent studies have highlighted the role of PIK3CA, RASA1, and TEK mutations in the development of vascular malformations, shifting the classification paradigm from a purely anatomical and physiological model to a molecular one. Boscolo et al. [12] demonstrated that PIK3CA mutations are common in overgrowth syndromes, supporting the use of PI3K inhibitors as a targeted therapeutic strategy. Similarly, Vahidnezhad et al. [7] identified TEK (TIE2) mutations as a significant factor contributing to venous malformations by disrupting endothelial signaling. These findings build on earlier studies by Luks et al. [6], which first established the

genetic basis of lymphatic and venous malformations, paving the way for targeted therapies. However, despite these advancements, genotype-phenotype correlations remain incompletely understood, necessitating further research to refine treatment strategies and improve precision medicine applications.

Advancements in diagnostic imaging have significantly improved the detection and characterization of vascular malformations. Doppler ultrasound, MRI, and digital subtraction angiography (DSA) remain the gold standards for differentiating between low-flow and high-flow lesions. Greene et al. [1] emphasized that MRI with contrast enhancement provides superior soft tissue visualization, which is particularly useful in identifying mixed malformations. Meanwhile, DSA remains indispensable for arteriovenous malformations, as it offers real-time vascular mapping, aiding in treatment planning for embolization. Compared to traditional diagnostic techniques, genetic testing has emerged as a valuable complementary tool, enabling personalized treatment selection, especially in cases linked to PIK3CA and RASA1 mutations. This genetic insight has transformed the approach to vascular malformation management, allowing for a shift from symptom-based treatment to precision medicine approaches.

Historically, sclerotherapy and embolization were the primary treatments for venous and lymphatic malformations, offering effective symptom relief. However, these methods are associated with recurrence and incomplete resolution, particularly in large or infiltrative lesions. The introduction of targeted molecular therapies has significantly altered treatment strategies. Sirolimus (an mTOR inhibitor) has shown promising results in managing PIK3CA-related vascular anomalies, as it modulates abnormal cell proliferation. Similarly, Alpelisib (a PI3K inhibitor), which is currently under clinical trials, offers potential benefits for PROS-associated malformations. These therapies represent a shift from symptom control to disease modification, which could lead to more effective long-term outcomes. Nevertheless, additional clinical research is required to determine their long-term safety and effectiveness.

Given the chronic and recurrent nature of vascular malformations, a multidisciplinary team approach remains essential for optimizing patient outcomes. The management of vascular anomalies requires collaboration between specialists, including dermatologists, interventional radiologists, geneticists, and surgeons, to provide comprehensive and patient-specific treatment. Furthermore, psychosocial support plays a significant role, particularly in pediatric patients with visible malformations, which can impact self-esteem and quality of life. Smolak et al. [13] emphasized that body image concerns can emerge as early as age six, highlighting the need for counseling and psychological interventions as part of holistic patient care.

Despite significant progress in classification, diagnosis, and treatment, several challenges remain unresolved. The incomplete understanding of genotype-phenotype correlations limits the full potential of precision medicine in vascular malformations. Large-scale clinical trials are also necessary to confirm the long-term safety and effectiveness of innovative targeted medicines. Another challenge is the limited accessibility of genetic testing and advanced imaging in resource-constrained settings, which may hinder early diagnosis and timely intervention. Future research should focus on expanding genetic databases to refine mutation-specific treatment strategies, developing combination therapies that integrate molecular inhibitors with interventional procedures, and improving global access to advanced diagnostics and targeted treatments.

In conclusion, this review highlights the significant impact of genetic discoveries, advanced imaging techniques, and targeted molecular therapies in the management of vascular malformations. While conventional treatments remain valuable, the integration of molecular insights and precision medicine is transforming the field. A multidisciplinary, patient-centered approach is crucial to enhancing diagnostic accuracy, therapeutic efficacy, and long-term patient outcomes. Further research and clinical advancements are needed to bridge existing gaps and improve the standard of care for individuals affected by vascular malformations.

Conclusion

Advances in molecular genetics have significantly improved our understanding of the pathogenesis of vascular malformations, with mutations in PIK3CA, TEK, and RASA1 playing a crucial role in disease development. These genetic insights have led to the development of targeted therapies, such as Sirolimus and Alpelisib, which offer promising alternatives to conventional treatments like sclerotherapy and embolization. Large-scale clinical trials are necessary to confirm the long-term safety and efficacy of these innovative treatments, even if they mark a paradigm shift in management.

Despite these advancements, challenges remain in standardizing treatment protocols, assessing long-term outcomes, and ensuring accessibility to genetic testing and advanced diagnostics. Future research should focus on refining molecular classification, optimizing therapeutic strategies, and enhancing patient-specific treatment approaches. A multidisciplinary framework, involving geneticists, radiologists, dermatologists, and surgeons, is essential to improving diagnostic accuracy, treatment efficacy, and the general well-being of those who suffer from vascular abnormalities.

Limitations

This review is based solely on previously published literature, and no new experimental or clinical data were generated. As a result, conclusions rely on the quality, consistency, and methodologies of existing studies, which vary in sample size, diagnostic criteria, and classification systems. These inconsistencies may pose challenges in directly comparing findings across different studies.

Additionally, while emerging targeted therapies, such as Sirolimus and Alpelisib, have shown promising results, long-term safety and efficacy data remain limited. The potential for recurrence and adverse effects warrants further investigation through large-scale, longitudinal studies.

Another challenge is the lack of a universal consensus on the optimal therapeutic approach. Treatment protocols vary significantly across institutions and geographic regions, leading to potential disparities in patient outcomes. Furthermore, while high-resolution imaging and genetic testing are crucial for accurate diagnosis and treatment planning, their limited availability in resource-constrained settings increases the risk of misdiagnosis or suboptimal management. Addressing these gaps through global collaboration and research is essential for improving the overall management of vascular malformations.

Recommendations

Encouraging international collaborations among researchers, clinicians, and geneticists can accelerate advancements in vascular malformation research. Quality-of-life assessments should be incorporated into research to evaluate the long-term psychological and functional impacts of various treatments. Open-access databases should be developed to facilitate data sharing on genetic variants, treatment responses, and clinical outcomes for improved evidence-based decision-making.

Source of funding

There was no source of funding.

Conflict of interest

There was no conflict of interest.

Registration and protocol

This systematic review was not registered in a public registry such as PROSPERO, and a formal review protocol was not prepared before the commencement of the review.

Availability of data, code, and other materials

The following materials are available upon reasonable request from the corresponding author: template data collection forms, extracted data from included studies, data used for analysis, summary risk of bias assessments, and references for all included articles. No analytic code or software scripts were generated as part of this review.

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