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Review Article

Peripheral Venous Malformations: A Narrative Review Linking Phenotype, Genotype, and Pain-Directed Treatment

Prof. em. Dr. med. I. Baumgartner*

Internal Medicine & Vascular Medicine, Co-Founder, Vasc Alliance AG, Schänzlihalde 13013 Bern, Switzerland

***Corresponding author**

Prof. em. Dr. med. I. Baumgartner, Internal Medicine & Vascular Medicine, Co-Founder, Vasc Alliance AG, Schänzlihalde 13013 Bern, Switzerland, Tel: 41 31 335 31 50

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Abstract

Venous malformations (VM) are the most common congenital vascular anomaly and a frequent cause of chronic pain, yet clinical decision-making is often guided by isolated pieces of evidence rather than an integrated understanding of the disease. This narrative review synthesizes four studies conducted within a single-center, prospectively maintained vascular malformation registry (VASCOM, Bern, Switzerland, 2008-2022) to outline a coherent framework spanning phenotype, anatomical classification, genotype, and treatment outcome. In a cohort of 558 adolescent and adult patients with congenital vascular malformations, simple VM was the most common subtype and pain was the leading presenting symptom, with distinct complication patterns across malformation types. A revised phlebographic classification distinguishing non-lacunar from lacunar internal venous architecture was validated with high inter-reader reliability and carries direct implications for sclerotherapy dosing and technique selection. Genetic characterization of the same source population identified somatic *PIK3CA* variants in a subset of tested patients; non-hotspot variants were associated with higher variant allele frequency and were more common in syndromic presentations, underscoring the incomplete correlation between genotype and phenotype. Finally, a comparative cohort study of 227 patients demonstrated that alcohol embolization produced faster and more pronounced relief of mean and minimal pain than non-invasive management, but conferred no statistically significant advantage for maximal pain, at a minor (8%) and major (6%) complication rate. Considered together, these findings argue against a one-size-fits-all approach to VM and support a stepwise pathway that integrates phenotypic recognition, anatomical characterization, selective genetic testing, and shared decision-making about invasive versus conservative pain management, anchored by disease-specific, patient-reported outcome measures rather than pain or imaging alone.

INTRODUCTION

Venous malformations are slow-flow congenital vascular anomalies arising from errors in vascular morphogenesis, with an estimated incidence of 1 to 2 per 5,000 births and a prevalence of approximately 1.5% in Western populations [1]. Although present from birth, they typically grow proportionately with the child, do not regress spontaneously, and frequently become clinically apparent only later in life, when swelling, disfigurement, coagulopathy, or most commonly pain prompt medical attention [2].The International Society for the Study of Vascular Anomalies (ISSVA) classification provides a shared biological vocabulary for these lesions [3], yet classification of malformation type alone does not capture the substantial heterogeneity in clinical presentation, underlying somatic genetics, internal vascular architecture, or expected response to treatment that clinicians encounter at the bedside.

This heterogeneity has practical consequences. Two patients with an identical ISSVA diagnosis of "venous malformation" may differ markedly in the tissues involved, the presence of associated syndromic features, the internal structure of the malformation on direct puncture phlebography, the somatic mutation driving lesion growth, and, ultimately, in how much relief they can expect from a given treatment. Historically, the efficacy of the most established invasive treatment, alcohol (ethanol) embolization, has been judged primarily by radiological reduction in malformation size, a metric that correlates only loosely with what matters most to patients, pain and functional impairment.

Over the past decade, our group has approached these gaps through a single, prospectively maintained institutional registry. Successive analyses of this registry have addressed, the clinical phenotype of the full malformation spectrum, a refined anatomical classification of venous malformations based on phlebography, the somatic genetic landscape of *PIK3CA*-related lesions, and a comparative evaluation of alcohol embolization against

non-invasive management for pain relief. Each of these four studies has previously been published as a stand-alone report. The aim of the present narrative review is not to reproduce their data, but to synthesize their findings into a single, clinically usable framework, and to identify where the four pillars, phenotype, anatomy, genotype, and treatment outcome, inform one another, and where important gaps remain. No additional literature databases were systematically searched and no new statistical analysis was performed. This is a narrative, not a systematic, review, and its scope is deliberately anchored in a single, well-characterized cohort rather than in the broader international literature, which is cited here only to provide context.

THE VASCOM REGISTRY

All four studies summarized below draw on overlapping subsets of the same source population: consecutive patients with congenital vascular malformations referred to the multidisciplinary Vascular Malformation Center at the University Hospital of Bern and enrolled in an institutional registry since 2008. Diagnoses were established using a multimodal approach combining clinical examination, duplex ultrasound, magnetic resonance imaging, and, where an invasive procedure was planned, direct puncture phlebography. All patients gave informed consent for anonymized use of their data, and each individual study was separately approved by the Cantonal Ethics Committee of Bern. Because the four analyses drew on different eligibility windows, follow-up requirements, and sub-cohorts (ranging from 67 to 558 patients), the total patient numbers are not additive across studies. Where relevant, this is noted below. Table 1 summarizes the design and principal finding of each study before they are discussed in turn.

THE CLINICAL PHENOTYPE SPECTRUM

The first pillar of this framework is a systematic description of phenotype. Tuleja and colleagues analyzed 457 adolescent and adult patients (mean age 35 years; 56% female) consecutively enrolled between 2008 and 2021, applying the ISSVA framework to classify each malformation as simple, combined, or associated with other anomalies (syndromic) [4]. Simple malformations accounted for the large majority of cases (79%), with combined and syndromic forms making up 6% and 15%, respectively. Within this spectrum, venous malformations were both the most common congenital vascular malformation overall (52%) and the most common simple subtype (66%), consistent with epidemiological data from other cohorts [5].

Pain emerged as the single most frequent presenting symptom across all malformation types, though its intensity varied by subtype. It was more pronounced in patients with simple venous and arteriovenous malformations than in other groups, consistent with prior reports linking pain to localized intravascular coagulopathy and mechanical distension of dysplastic venous channels [6]. Beyond pain, the study highlighted clinical problems that clustered by malformation type rather than occurring uniformly. Bleeding and skin ulceration were characteristic of arteriovenous malformations, localized intravascular coagulopathy, reflected in elevated D-dimer levels, was characteristic of venous malformations [7], and infectious complications predominated in lymphatic malformations. Limb-length discrepancy was substantially more frequent among patients with malformations associated with other anomalies than among those with simple or combined lesions (22.9% vs. 2.3%; P<.001), and soft-tissue overgrowth was present in roughly one-quarter of all patients, independent of ISSVA subgroup.

Clinically, these findings carry two implications that recur throughout this review. First, pain cannot be treated as a generic symptom of "having a venous malformation". It is shaped by the tissues involved, the presence of coagulopathy, and, as discussed below, potentially by the underlying somatic mutation. Second, the co-occurrence of limb-length discrepancy, soft-tissue overgrowth, or multifocal disease with a venous or

Table 1: Overview of the four registry-based studies synthesized in this review

Study	Design and cohort	Focus	Key finding(s)
Tuleja et al, 2023 [4]	Retrospective, n=457 (2008-2021)	Clinical phenotype across the vascular malformation spectrum	Venous malformation was the most common subtype (52%); pain was the leading symptom overall; complication pattern differed by malformation type
Bernhard et al, 2024 [9]	Retrospective, n=67 evaluable phlebograms (2009-2018)	Anatomical (phlebographic) classification	Non-lacunar vs. lacunar internal architecture distinguished with excellent inter-reader reliability (κ=0.91); proposed addition to the established drainage-based classification
Andreoti et al, 2025 [13]	Cross-sectional genetic analysis, n=25 *PIK3CA*-positive of 89 tested (2008-2022)	Genotype-phenotype correlation	Non-hotspot *PIK3CA* variants showed higher variant allele frequency and were more frequent in syndromic disease
Tuleja et al, 2025 [18]	Retrospective comparative cohort, n=227 (2008-2022)	Comparative pain outcome	Alcohol embolization improved mean and minimal pain faster than conservative care; no significant advantage for maximal pain; overall minor (8%) and major (6%) complication rate

lymphatic malformation should raise clinical suspicion for a syndromic, *PIK3CA*-related overgrowth disorder and prompt referral for genetic evaluation, rather than being dismissed as an incidental finding. In this sense, careful phenotyping functions as the entry point of the diagnostic and therapeutic pathway proposed at the end of this review, rather than as a descriptive exercise in its own right.

REFINING ANATOMICAL CLASSIFICATION FOR TREATMENT PLANNING

While phenotype defines what type of malformation a patient has, it says little about how that malformation will behave once punctured and injected with a sclerosing agent. The established Puig classification categorizes venous malformations by their venous drainage pattern into four types, ranging from lesions with no visible drainage (type I) to those draining into an already ectatic deep venous system (type IV) [8]. This classification has guided embolo-sclerotherapy planning for two decades, but it does not describe the internal architecture of the malformation itself. Information that, in clinical experience, strongly influences how a sclerosant behaves once injected.

Bernhard and colleagues addressed this gap by retrospectively reviewing direct puncture phlebograms obtained in patients treated with embolo-sclerotherapy between 2009 and 2018 [9]. Of 92 phlebograms initially identified, 67 were of sufficient quality for independent, blinded assessment by two experienced readers, who classified each malformation's internal angioarchitecture as either non-lacunar (predominantly small, reticular dysplastic channels) or lacunar (predominantly large, ectatic venous spaces), using an 80% visual threshold. This distinction proved highly reproducible, with 96% inter-reader agreement (κ=0.91). A level of reliability that exceeded even that of the established drainage-based classification itself (87% agreement, κ=0.78). Combining both parameters into a single, adjusted classification (e.g., type IIa vs. type IIb) preserved substantial reliability (82% agreement, κ=0.77) without added complexity for the reader. In this cohort, lacunar morphology was more common than non-lacunar morphology (61% vs. 39%), and there was a non-significant trend toward higher D-dimer levels in lacunar lesions, consistent with the known association between large venous lacunae and localized intravascular coagulopathy [7].

The clinical rationale for this distinction is straightforward, sclerosant effectiveness depends on adequate contact between the agent and the endothelium, together with sufficient dwell time. In non-lacunar, small-channel malformations, ethanol or other sclerosants achieve close endothelial contact and can be expected to produce more complete occlusion, whereas in lacunar, ectatic malformations, the same volume of sclerosant is diluted across a larger space, reducing endothelial contact and effectiveness, and increasing the risk that the agent will be washed out into the systemic circulation before it can act. A mechanism directly relevant to the complication profile discussed below. In practice, interventionalists have long adjusted technique intuitively (for instance, combining coils with sclerotherapy in large lacunar lesions), but a validated, reproducible vocabulary for this distinction allows such adjustments to be planned prospectively, taught systematically, and, eventually, correlated with outcome and with the somatic genotype discussed next.

GENETIC UNDERPINNINGS: PIK3CA AND BEYOND

Most venous malformations arise from postzygotic, mosaic gain-of-function mutations that constitutively activate endothelial signaling. Two pathways account for the great majority of cases: activating mutations in the angiopoietin receptor gene *TEK*, identified in both solitary and multifocal sporadic venous malformations [10], and activating mutations in *PIK3CA*, the catalytic subunit of phosphoinositide 3-kinase, which drive a broad spectrum of venous, lymphatic, and combined overgrowth phenotypes via the PI3K-AKT-mTOR pathway [11,12]. Because these mutations are somatic and mosaic, present only in the malformed tissue and often at low allele fraction, genotype-phenotype correlation has remained imperfect. Identical mutations can produce different clinical pictures, and different mutations can converge on similar phenotypes.

Andreoti and colleagues examined this correlation directly, testing biopsy material from patients with available genetic results (using a next-generation sequencing panel introduced into clinical practice in October 2020) for *PIK3CA* variants [13]. Among 89 patients with results available by mid-2022, 25 carried a *PIK3CA* variant, 16 with a simple or combined (non-syndromic) vascular malformation, and 9 with a malformation associated with other anomalies (syndromic). Sixteen of the 25 patients carried one of four recurrent "hotspot" variants located in exons 9 and 20 of *PIK3CA*, at a relatively low variant allele frequency (0.9-9.7%). The remaining nine carried one of five distinct non-hotspot variants, at a markedly higher and more variable allele frequency (3.6-31.7%). Two findings stood out statistically. Non-hotspot variants were associated with significantly higher variant allele frequency than hotspot variants (P=.0253), and

were significantly more frequent among patients with syndromic, rather than non-syndromic, malformations (P=.0034).

These results have two practical implications. First, allele frequency and, by extension, the proportion of mosaic cells within a biopsy, appears to track with phenotypic severity, offering a partial biological explanation for why some patients with a *PIK3CA*-driven lesion develop overgrowth or multi-tissue involvement while others do not. Second, from a diagnostic standpoint, non-hotspot variants are easily missed by genetic panels designed primarily to detect recurrent hotspot mutations, Clinicians evaluating a patient with a syndromic phenotype, particularly with limb-length discrepancy or soft-tissue overgrowth, as characterized in the phenotype cohort above, should ensure that genetic testing is broad enough to capture the full coding sequence of *PIK3CA*, rather than being restricted to hotspot-only assays.

Beyond diagnostic classification, this genetic layer is becoming directly actionable. The mTOR inhibitor sirolimus has demonstrated efficacy across a range of complicated vascular anomalies, including *PIK3CA*- and *TEK*-related malformations [14], and PI3K-pathway inhibitors developed for oncologic indications are increasingly repurposed for *PIK3CA*-related overgrowth spectrum disorders [15]. For now, these molecularly targeted therapies remain reserved for complicated or refractory disease rather than first-line pain management, but they represent the most plausible future complement, rather than replacement, to the mechanical treatments discussed next, particularly for the syndromic subgroup identified through the phenotype-genotype correlation described here.

COMPARATIVE OUTCOMES: ALCOHOL EMBOLIZATION VERSUS NON-INVASIVE MANAGEMENT FOR PAIN

The technical efficacy of alcohol (ethanol) embolization in reducing venous malformation size is well established and has been repeatedly confirmed in meta-analyses of sclerosing agents [16,17]. What has remained far less clear is whether this technical, radiological success translates into superior pain relief compared with non-invasive management, and whether the natural fluctuation and adaptation of chronic pain over time, rather than the intervention itself, explains apparent improvement. Addressing this question requires a comparator arm, which most embolization series lack.

Tuleja and colleagues addressed this directly in a retrospective, comparative cohort study conducted between 2008 and 2022 [18]. Of 227 patients with peripheral venous malformations who met inclusion criteria, 86 had undergone at least one alcohol embolization (the intervention group) and 141 had received non-invasive management only, compression garments, physical or ergotherapy, and, where indicated, short-course anticoagulation for localized thrombosis (the control group). Pain was recorded at every visit using the 0-10 Numerical Rating Scale, separately for maximal, mean, and minimal pain, and the primary analysis compared the change in each pain domain from the initial visit to the follow-up visit closest to one year (but no later than two years). Because treatment allocation was not randomized, patients and physicians jointly decided on embolization versus conservative management, after discussing potential harms and benefits, the analysis used inverse probability of treatment weighting to adjust for baseline imbalances in malformation extent, hypertrophic tissue, history of thrombophlebitis, age, and baseline pain level, an approach well suited to approximating a randomized comparison from observational data [19].

At baseline, patients selected for embolization reported higher pain across all three domains than those managed conservatively, consistent with clinicians reserving invasive treatment for more symptomatic disease. After weighting, both groups showed comparable adjusted baseline pain, allowing a fair comparison of trajectories over time. For the primary endpoint, maximal pain, both groups improved substantially over the course of one year. The conservatively managed group's maximal pain fell by roughly 0.95 points on the 10-point scale, and the embolization group's maximal pain fell by a further, non-significant 0.99 points beyond that (P=.12). In other words, non-invasive management alone produced a clinically meaningful reduction in peak pain episodes, and embolization did not confer a statistically demonstrable additional benefit for this domain, a finding that runs counter to the implicit assumption, in much of the interventional literature, that mechanical occlusion of the malformation is required to control severe pain.

For the two secondary endpoints, the picture differed. Mean, "background" pain fell only modestly with conservative management alone (approximately 0.44 points per year) but fell by a further, statistically significant 1.06 points per year in the embolization group (P=.02); similarly, minimal pain, the pain present even during good periods, fell only slightly with conservative management (0.12 points) but by a further significant 0.69 points with embolization (P=.01), although this smaller absolute difference likely reflects a floor effect, since minimal pain scores were close to zero in both groups by

one year. Neither gender, age, nor a history of previous treatment modified the effect of embolization on pain trajectories, arguing against the need to select candidates for embolization on these grounds alone.

Complications occurred in 12 of 86 treated patients (14%). Most were transient and required no further intervention. Local swelling and pain in four patients, hypoesthesia in two, and paresthesia in one. Five patients experienced a major complication, a flexion deficit requiring surgical adhesiolysis, asymptomatic femoral osteonecrosis, deep venous thrombosis, skin necrosis at the injection site, and nerve paralysis leading to chronic motor deficit, respectively, each occurring in a single patient. There were no deaths and no pulmonary embolism or pulmonary vasospasm, and the overall complication rate was in line with recent multi-agent sclerotherapy series reporting rates around 11-12%.

Taken together, these results reframe how alcohol embolization should be discussed with patients. It is not a treatment that reliably prevents severe pain flares beyond what conservative measures already achieve. Rather, its principal, statistically demonstrable benefit is a faster and more pronounced reduction in the everyday, background burden of pain, the pain that shapes quality of life between flares, at the cost of a real, if generally manageable, 14% complication rate. This supports a shared decision-making approach in which non-invasive measures are offered first and given a genuine trial of at least a year, with escalation to embolization considered for patients whose pain is dominated by a persistent background component, rather than intermittent peaks, or who fail to improve on conservative management, rather than positioning embolization as a default first-line intervention. Whether the lacunar/non-lacunar distinction described above, or the underlying somatic mutation, predicts which patients will respond preferentially in the mean- or minimal-pain domain is an open question that the present cohort was not designed and was likely underpowered - to answer, but it represents a natural next step for prospective work that links the anatomical and genetic pillars of this framework directly to treatment response.

TOWARD AN INTEGRATED, PATIENT-CENTERED PATHWAY

Read individually, each of the four studies summarized here answers a well-defined question. Read together, they outline a pathway that we believe should structure the management of peripheral venous malformations more explicitly than current practice generally allows.

The pathway begins with careful phenotyping at first presentation. Documenting not only the ISSVA subtype but also the tissues involved, the presence of coagulopathy, and any signs - limb-length discrepancy, soft-tissue overgrowth, multifocality, that should trigger genetic evaluation for a syndromic, *PIK3CA*-related disorder. For patients in whom an invasive procedure is being considered, direct puncture phlebography should record not only venous drainage but also internal angioarchitecture (non-lacunar vs. lacunar), since this single, highly reproducible parameter carries direct implications for expected sclerosant dose, technique, and probability of complete occlusion. Where genetic testing is pursued, panels should be broad enough to capture non-hotspot *PIK3CA* variants, which are both more common in syndromic disease and more likely to be missed by hotspot-restricted assays. Finally, the choice between non-invasive management and alcohol embolization should be framed not as "intervention versus nothing," but as a decision about which pain domain matters most to the individual patient, background, everyday pain versus infrequent severe flares, since the evidence base for benefit differs materially between the two.

A recurring limitation across all four studies, and one this review does not resolve, is the almost exclusive reliance on a single, generic outcome measure, the Numerical Rating Scale for pain, to judge success. Pain is necessary but not sufficient. It captures neither the aesthetic and psychosocial burden of visible malformations nor the functional impairment that patients frequently describe as most disabling. The disease-specific Outcome measures for VAscular MAlformations (OVAMA) instrument was developed precisely to close this gap, covering symptoms, appearance, and treatment satisfaction in a single, validated tool [20], and has been proposed for use alongside generic instruments such as the Patient-Reported Outcomes Measurement Information System (PROMIS), which captures broader domains of physical function, mobility, and emotional well-being [21]. A systematic review of available instruments for vascular malformations found substantial heterogeneity in measurement properties and concluded that no single tool yet captures the full range of relevant outcomes, reinforcing the case for combining a disease-specific and a generic instrument rather than relying on either alone [22]. Notably, even where a treatment produces a statistically significant change on the Numerical Rating Scale, as embolization did for mean and minimal pain in the comparative study above, it remains unclear whether that change exceeds the minimal clinically important difference established for pain scales in other conditions [23], since this threshold has not been formally validated in venous malformations specifically.

Looking forward, the most promising direction is not

simply to describe phenotype, anatomy, genotype, and outcome in parallel, as the four studies summarized here necessarily did, but to test them jointly and prospectively, does lacunar morphology or *PIK3CA* mutation status predict which patients will respond preferentially to embolization in the mean-pain domain rather than the maximal-pain domain? Would molecularly targeted agents [24], deployed earlier in genetically characterized syndromic patients, reduce the eventual need for repeated mechanical embolization and its associated complication rate? These questions require prospective, adequately powered, ideally multi-center cohorts - a natural extension of existing collaborative networks for vascular anomalies, that collect phenotype, phlebographic architecture, genotype, and disease-specific patient-reported outcomes within the same patients from the outset, rather than reconstructing the picture retrospectively across separate analyses, as the present review has attempted to do.

CONCLUSION

Peripheral venous malformations are not a single, homogeneous entity, and a decade of work within a single, well-characterized registry illustrates why a one-size-fits-all approach to their management falls short. Careful phenotyping identifies which patients warrant genetic evaluation; phlebographic characterization of internal architecture informs how an intervention should be planned and dosed; genetic testing, broad enough to detect non-hotspot *PIK3CA* variants, refines diagnosis in syndromic disease and points toward future molecularly targeted therapy; and a genuinely comparative evaluation of alcohol embolization against non-invasive management shows that the two approaches are not interchangeable, but rather address different components of the pain experience. None of these four pillars, taken alone, is sufficient to guide an individual treatment decision; taken together, they support a stepwise, shared decision-making pathway rather than a default recommendation for or against intervention. Realizing the full potential of this framework will require prospective studies that collect phenotype, anatomy, genotype, and disease-specific patient-reported outcomes within the same patients, allowing the correlations proposed here to be formally tested rather than inferred across separate cohorts.

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