OPEN

Journal of Vascular Anomalies
An open access multidisciplinary journal
ISSVA

# Prevalence and Risk Factor Analysis of Leg Length Discrepancy in Patients with a Capillary Malformation on the Lower Extremities

## *A Retrospective Cohort Study*

Besiana P. Beqo[a], Isabella R. Plumptre[a], Kimya Hassani-Ardakani[b], Samantha A. Spencer[a,c], Marilyn G. Liang[a,b]

**Abstract**

**Objective:** The study aimed to determine the prevalence of major leg length discrepancy (LLD ≥2 cm) among patients with lower-limb capillary malformation (CM) and to identify the risk factors that influence LLD development.

**Methods:** This retrospective cohort study included patients with lower-limb CM, such as regional CM (RCM), capillary venous malformation (CVM), diffuse CM (DCM), and CM-arteriovenous malformation. LLD was evaluated using physical and radiographic methods. Detailed descriptive analysis was performed. Regression analysis was used to investigate risk factors, while Kaplan–Meier analysis estimated the progressive risk of developing LLD by age 15.

**Results:** We included 1,008 patients with a lower-limb CM, categorized as regional CM (n=710, 70.4%), capillary venous malformation (n=121, 12.0%), DCM (n=128, 12.7%), and CM-arteriovenous malformation (n=49, 4.9%). Major LLD developed in 14.8% of cases, with the highest incidence observed among patients with DCM (44.5%). Kaplan–Meier analysis estimated a 31.4% overall progressive risk of developing major LLD by age 15, rising to 66.4% in the DCM group. Significant LLD predictors included DCM subtype, proximal CM location (odds ratio [OR], 1.40; 95% confidence interval [CI], 1.09–1.83; *P* = .01), full-length leg involvement (OR: 7.00, 95% CI: 4.83–10.02, *P* < .001) and combined medial and lateral side involvement (OR: 6.73, 95% CI: 3.69–12.4, *P* < .001).

**Conclusion:** Major LLD is common in children with lower extremity CM, particularly in those with DCM. Significant predictors of major LLD include larger affected areas, proximal location, full-length leg extent, and combined medial and lateral position. Early and accurate identification of these risk factors is crucial for timely surgical intervention.

**Keywords:** Leg length discrepancy, capillary malformation, regional capillary malformation, capillary venous malformation, diffuse capillary malformation, capillary malformation-arteriovenous malformation

*[a]Vascular Anomalies Center, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts; [b]Department of Dermatology, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts; and [c]Department of Orthopedic Surgery, Boston Children's Hospital and Harvard Medical School, Boston, Massachusetts*

*Financial Disclosure: The authors declare that they have no conflicts of interest with regard to the content of this report.*

*Previous Presentations: This research was presented in poster format at the 2024 International Society for the Study of Vascular Anomalies World Congress; May 8, 2024; Madrid, Spain.*

SDC *Supplemental digital content for this article is available at www.jovaopen.org.*

*Correspondence: Marilyn G. Liang, MD, Department of Dermatology, Vascular Anomalies Center, Boston Children's Hospital, 300 Longwood Ave, Boston, MA 02115 (marilyn.liang@childrens.harvard.edu).*



*Journal of Vascular Anomalies (2025) 6:e130*

*Received: 14 May 2025; Accepted 17 September 2025*

*Published online 20 November 2025*

*DOI: 10.1097/JOVA.0000000000000130*

## Introduction

Capillary malformations (CM) are the most common congenital vascular birthmarks occurring in approximately 0.3%–0.5% of newborns.[1,2] They are visible at birth as persistent pink or red patches and can range in extent from small localized skin changes to large lesions encompassing multiple segments of a limb. Although CMs are often considered primarily a cutaneous finding, they can be associated with soft-tissue or skeletal abnormalities. In the lower extremities, these malformations may lead to musculoskeletal alterations, including undergrowth or overgrowth, which can manifest as leg length discrepancy (LLD) (Figure 1).[1–5]

LLD, defined as a difference in length between the 2 lower limbs, becomes clinically significant (major) at a threshold of 2 cm or more.[6] When unrecognized or untreated, significant LLD can affect posture, gait, and load distribution, predisposing children to chronic pain, progressive scoliosis, and early osteoarthritis.[7–9] Such discrepancies are comparatively rare in the general pediatric population,[10] but they frequently appear as sequelae of vascular malformations.[3–5]

Despite growing recognition of the link between CM lesions of the lower extremities and LLD, many questions remain about the precise mechanisms driving skeletal over- or undergrowth and about which patients will progress to a clinically meaningful discrepancy.[4] Timely intervention, often via epiphysiodesis, is crucial for effectively mitigating major LLDs.

Epiphysiodesis typically involves arresting growth in the longer limb to allow the shorter one to catch up and is generally associated with low complication rates.[11] Although no single study conclusively defines it, a projected discrepancy of 2 cm or more at maturity is a widely accepted clinical indication for epiphysiodesis to treat or prevent LLD in a growing child (Figure 2).[6,10–14] However, because the time window for this intervention is narrow, delayed or missed diagnoses may limit its effectiveness or prevent its usage altogether.[11]

This study aimed to determine the prevalence of major LLD (≥2 cm) by age 15 in children with lower extremity CM and to identify potential risk factors for LLD development in this population. Given the limited existing data on predictors of LLD in patients with CM, our analysis was exploratory and hypothesis-generating. Age 15 was chosen as a clinically relevant endpoint because growth plates typically begin closing around this age range (14–18 years for girls and 16–20 years for boys), making it a crucial period for identifying and intervening on major LLD before skeletal maturity. We also evaluated foot overgrowth as a secondary outcome due to its clinical relevance and potential to co-occur with or mimic LLD-related gait imbalance.

## Methods

### Study design and overview

In this single-center, retrospective cohort study, we included patients of any age diagnosed with lower-limb CM at the Vascular Anomalies Center or the Orthopedic Department of Boston Children's Hospital from January 2000 to December 2022. This study aimed to determine the prevalence of clinically important LLD by age 15 and identify potential risk factors for LLD in patients with leg CM.

### Patients and study measurements

CM cases were diagnosed and classified by a multidisciplinary clinical team in accordance with the International Society for the Study of Vascular Anomalies clinical and radiologic guidelines.[15] Genetic testing, often performed later based on clinical suspicion or patient preference, was not readily available. Previously, obtaining genetic testing was more difficult. Insurance coverage for genetic testing is not guaranteed. Included conditions were regional CM (RCM, defined as CM affecting 1 limb), diffuse CM (DCM) with or without associated tissue overgrowth (defined as CM affecting multiple limbs), capillary venous malformation (CVM), and CM-arteriovenous malformation (CM-AVM).

We excluded cases with incomplete medical records, unclear diagnoses, and other specific diagnoses and syndromic conditions that did not meet the study criteria for isolated or combined CM (Figure 3).

Conditions such as macrocephaly-CM (M-CM) and cutis marmorata telangiectatica congenita were excluded due to their distinct clinical profile, often involving complex systemic findings and widespread cutaneous marbling with overlapping syndromic features that could confound our LLD analysis. Conditions such as capillary lymphatic malformations, capillary–lymphatic venous malformation/Klippel-Trenaunay syndrome, and congenital lipomatous overgrowth, vascular malformations, epidermal nevi, and skeletal/scoliosis syndrome were not included in the analysis due to their widely heterogeneous presentations and the potential for confounding associated features. To address potential selection bias, we analyzed baseline demographic factors between cases excluded due to incomplete medical records and those included in the study, and found no

**Figure 1.** A 21-month-old boy with full-length left leg CM and 1.4 cm leg length discrepancy (left > right). The lesion spans multiple contiguous segments, involving the hip, thigh, knee, lower leg, ankle, and foot, and is therefore classified as a full-length, multi-segment, contiguous lesion. The CM is located on the left leg and involves both medial and lateral surfaces. CM indicates capillary malformation.

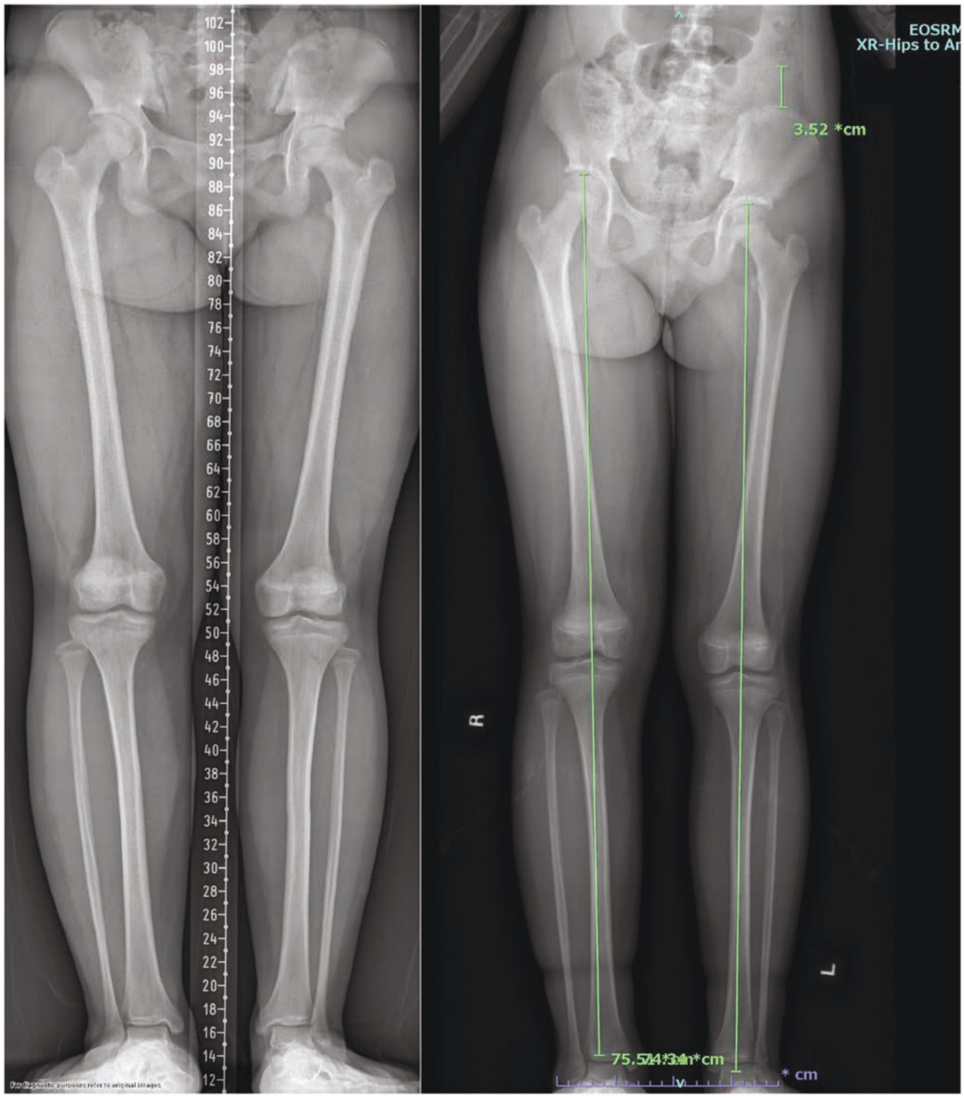



**Figure 2.** Anteroposterior bilateral lower extremity X-rays. Left panel: with a measurement ruler for scale. Right panel: without ruler, detecting a leg length discrepancy of 3.52 cm between the legs, with lengths of 75.54 cm and 84.8 cm, respectively.

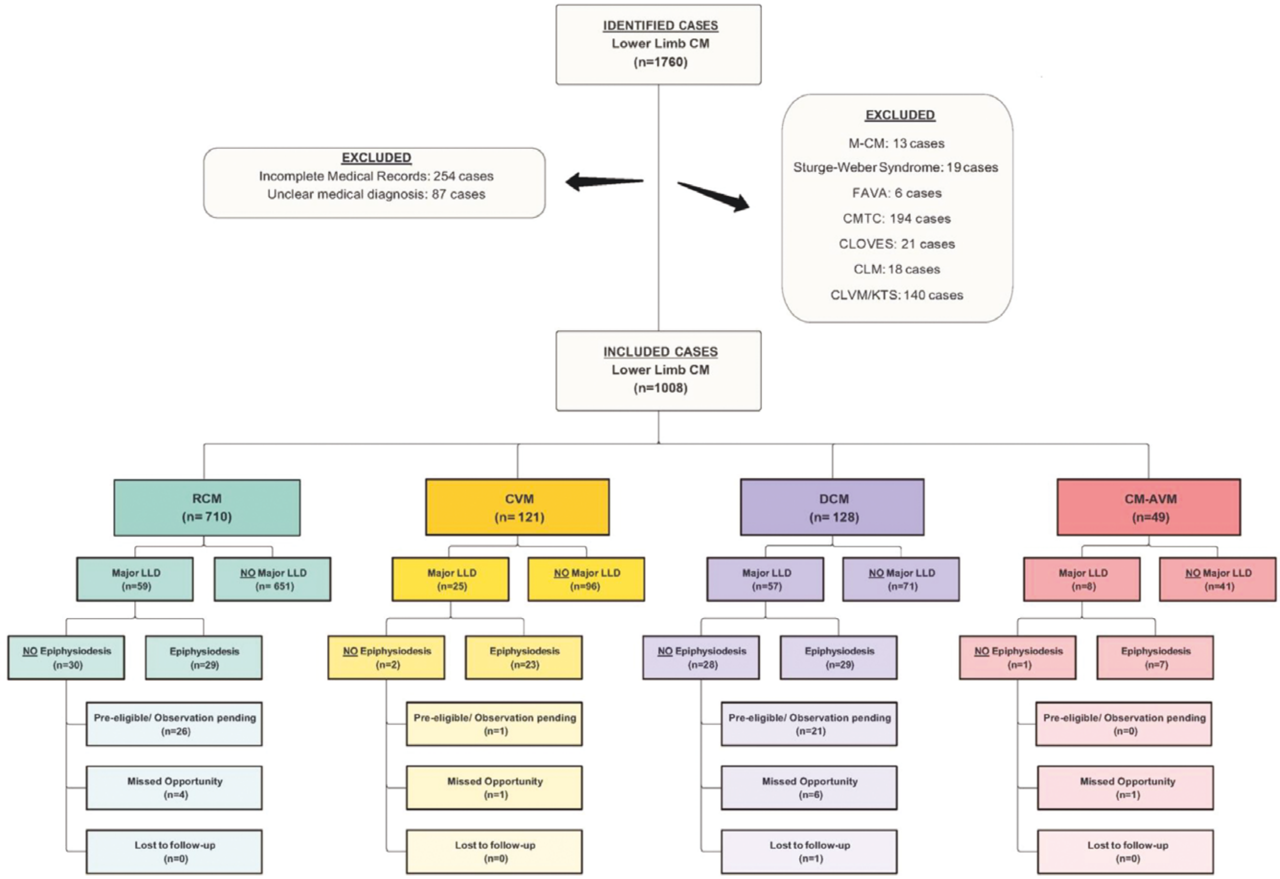
significant differences Supplemental Digital Table S1, https://links.lww.com/JV9/A53.

LLD was assessed in the clinic by 1 of 2 independent specialists using standard physical examination techniques, including direct measuring with a tape (from the anterior superior iliac spine to the medial malleolus) and indirect measuring with blocks. These methods were used for early screening and to guide further evaluation. When a discrepancy greater than 1 cm was suspected, radiographic confirmation was performed using scanograms or full-length standing alignment radiographs. Exact LLD measurements (cm) used in this study and reported in the analysis were obtained from radiographs to ensure consistency across the cohort. To accurately assess the clinical relevance of both larger discrepancies across all ages and smaller discrepancies in very young children, “major LLD” (ie, clinically important, also known as “significant LLD”) was defined as a discrepancy of 2 cm or more at any age, or between 1 cm and 2 cm in children 4 years old or younger. Foot overgrowth was noted when clinical documentation or imaging indicated asymmetry in foot size on the CM-affected side, as assessed by the treating specialist.

### *Data preparation*

Data were collected from the electronic medical record system, Cerner PowerChart, to identify lower extremity CM patients and extract relevant risk factor data. To verify and complete the dataset, we cross-checked each patient’s extracted data (clinical notes, radiologic records, and surgeon consultations) against the electronic medical record. Any discrepancies were resolved through a secondary review by 2 independent clinicians. CM leg variables were recorded via a standardized review of clinical notes, diagnostic images, and radiologic findings to determine the lesion’s location (hip, thigh, knee, lower leg, ankle, or foot), extent (full-length vs partial-length), and laterality (left, right, or bilateral). This process ensured consistent classification and minimized errors in lesion mapping.

Across 58 study variables, the majority (eg, sex, CM type, lesion characteristics, and key clinical outcomes) had either no missing values or fewer than 5 missing entries, translating to under 1% missingness for those fields. The remaining key study variables had fewer than 5% missing values. For continuous or ordinal variables, median imputation was used to maintain central tendencies, and for binary variables,




**n**: Number of cases
**M-CM**: Macrocephaly-Capillary Malformation
**FAVA**: Fibroadipose Vascular Anomaly
**CMTC**: Cutis Marmorata Telangiectatica Congenita
**CLOVES**: Congenital Lipomatous Overgrowth, Vascular malformations, Epidermal nevi, Spinal/skeletal anomalies
**CLM**: Capillary–Lymphatic Malformation
**CLVM/KTS**: Capillary–Lymphatic–Venous Malformation/Klippel-Trénaunay Syndrome
**CM**: Capillary Malformation
**RCM**: Regional Capillary Malformation
**CVM**: Capillary Venous Malformation
**DCM**: Diffuse Capillary Malformation
**CM-AVM**: Capillary Malformation-Arteriovenous Malformation
**LLD**: Leg Length Discrepancy

**Figure 3.** Flowchart of case selection and outcomes for lower extremity CM and associated major LLD. CLM indicates capillary lymphatic malformation; CLOVES, congenital lipomatous overgrowth, vascular malformations, epidermal nevi, spinal/skeletal anomalies; CLVM/KTS, capillary–lymphatic–venous malformation/Klippel-Trénaunay syndrome; CM, capillary malformation; CM-AVM, capillary malformation-arteriovenous malformation; CMTC, cutis marmorata telangiectatica congenita; CVM, capillary venous malformation; DCM, diffuse capillary malformation; FAVA, fibroadipose vascular anomaly; LLD, leg length discrepancy; M-CM, macrocephaly-capillary malformation; n, number of cases; RCM, regional capillary malformation.

missing entries were imputed as 0 (absence). Where applicable, K-nearest neighbors-based imputation was applied to categorical variables, preserving the underlying distribution. This multi-pronged approach is adopted to minimize bias and optimize data completeness for subsequent analyses.

We differentiated CM along the leg into 2 categories based on their extent. “Full-length leg involvement” described a lesion that spanned the entire leg length from the hip to the foot, including the hip, thigh, knee, lower leg, ankle, and foot. Conversely, “partial-length leg involvement” indicated lesions that were limited to certain areas of the leg without covering its full length. The “lesion segment count” variable captured the total number of distinct leg segments (hip, thigh, knee, lower leg, ankle, or foot) spanned by each CM lesion, serving as a practical proxy for lesion size. If multiple segments were affected, we also evaluated the lesion’s contiguity. Lesions that spanned adjacent leg segments without interruption were considered contiguous, whereas those separated by at least one unaffected region (eg, thigh and foot involvement but no knee or lower leg) were deemed noncontiguous. This approach provided a more precise characterization of the lesion's topographical distribution. A "proximity level" was used to quantify lesion proximity on the leg, with higher values indicating locations closer to the trunk, or more proximal points. Lower values represented more distal locations. For lesions spanning multiple leg locations, the highest proximity level among the affected areas was recorded. We acknowledge that the classifications used have not undergone formal validation. These approaches were introduced solely as practical, study-specific tools to facilitate comparative analyses in future research. A comprehensive list of variables used in this study is available in Supplemental Digital Table S2, https://links.lww.com/JV9/A53.

### *Summary statistics and statistical analysis*

Prevalence estimates were accompanied by 95% confidence intervals (CIs), calculated using the Wilson score method. Continuous variables were summarized with mean, standard deviation (SD), median, interquartile range (IQR), and range, while their distribution was assessed for normality using q-q plots. Stratification by CM types helped identify category-specific patterns. Associations between categorical variables were analyzed using Pearson's $\chi^2$ or Fisher exact test, with the latter's workspace expanded to $2 \times 10^9$. Monte Carlo simulations were used to generate *P* values for Fisher exact test, assessing associations among CM types and proximity levels. Differences in means and medians were analyzed using one-way analysis of variance and the Kruskal–Wallis rank sum test, respectively.

We assessed the risk of developing major LLD (≥2 cm) using logistic regression models, stratifying patients by CM subtype (RCM, CVM, DCM, CM-AVM) and incorporating these classifications as covariates. Whenever genetic test results were available, we integrated these data into our analyses, both univariate and multivariate as applicable, to explore potential associations with major LLD. We documented the proportion of patients tested, the type of genetic testing conducted, and the mutations identified, evaluating their predictive value for major LLD. Given the exploratory nature of this study, no formal correction for multiple comparisons was applied to the univariate analysis.[16,17] A multivariable logistic regression was performed to identify potential risk factors, initially including independent variables (Table 3), based on prior literature,[3,4,9,18,19] clinical relevance, and biologic plausibility. All variables were retained in their original form to preserve information and avoid arbitrary cutoffs; no continuous variables were dichotomized or recoded. In the multivariable analyses, we used a stepwise backward selection process, removing variables with a *P* value exceeding .05 to refine our model. Multicollinearity was assessed using variance inflation factors (all <4; Supplemental Digital Table S3, https://links.lww.com/JV9/A53). The model's fit was assessed using the Hosmer-Lemeshow test, and its predictive accuracy was evaluated through receiver operating characteristic curves and area under the curve values. Ordinal logistic regression was performed to examine the relationship between lesion proximity level and the likelihood of developing a major LLD. Kaplan–Meier survival analysis was performed to estimate the time-to-event probability of developing major LLD (≥2 cm) by age 15, complementing the logistic model by illustrating how risk accumulates over time. The proportional hazards assumption was tested with Schoenfeld residuals (*P* = .12), indicating no violations and supporting the validity of our time-to-event analysis. A *P* value of less than .05 was considered statistically significant for all analyses.

Data handling and statistical analysis were performed using R software ("R version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria").

This retrospective cohort study adhered to the Declaration of Helsinki and was approved by the local Institutional Review Board (Approval No. MB09-030158). Due to its retrospective design, individual informed consent was waived.

## Results

Our cohort consisted of 1008 patients with lower extremity CM, primarily RCM (70.4%, n = 710), followed by DCM (12.7%, n = 128), CVM (12.0%, n = 121), and CM-AVM (4.9%, n = 49) (Table 1). Females were slightly more prevalent (55.3%, n = 557), with no significant sex distribution differences among CM types. The median age at the last follow-up ranged from RCM at 7 years (IQR, 3–13 years) to CVM at 16 years (IQR, 10–22 years). Duration of follow-up for all types of CM averaged 5.4 years (SD: ±4.8 years), with a median duration of 4 years (IQR, 2–8 years) (Table 1).

Most CM lesions were limited to distinct segments of the leg. In the RCM group, 87.5% (n = 621/710) had partial-length-leg lesions. Full-length leg lesions were more common in the DCM group, affecting 70.3% (n = 90/128). No significant side preference (right versus left) was noted, and 32.8% (n = 42/128) of DCM patients had bilateral leg involvement. The lateral side of the leg was most commonly affected (68.5%, n = 690) across all CM types. The mean number of leg segments spanned by the malformation was 3.1 ± 2.3 overall, with DCM showing the highest involvement (6.6 ± 2.7; *P* < .001). Of those with multi-segment lesions, 57.9% (n = 584) were contiguous, and 13.7% (n = 138) were noncontiguous. Lesions more commonly affected proximal sites, particularly the hip (38.9%, n = 392) and thigh (30.6%, n = 308), with fewer cases at the knee (4.7%, n = 47) and lower leg (19.0%, n = 192). Ankle (3.2%, n = 37) and foot (3.7%, n = 37) involvement was less commonly seen.

An LLD of any size was present at birth in 11.2% (n = 113) of cases, especially in the DCM group (40.6%, n = 52/128) (*P* < .001). Among those who were not born with an LLD but subsequently developed a major LLD, 55% (n = 82/149) were first noted to have a discrepancy by a median age of 13 months (IQR, 1.5–24.0). The age at first documentation of any LLD varied significantly by CM type, with DCM and CM-AVM patients being the youngest at diagnosis, with median ages of 10 months (DCM: IQR, 0.0–18.0), (CM-AVM: IQR, 8.3–22.5), respectively (*P* < .001).

Among our cohort, 14.8% (95% CI, 13–17%) of participants (n = 149) developed a major LLD, including almost half of the patients with DCM (44.5%, n = 57/128) (*P* < .001). Among the 149 patients with major LLD, 21/149 (14.1%) had bilateral lower extremity CM and thus did not have a clearly "affected versus unaffected" side to compare. Of the remaining 128 patients, 106 (82.8%) had a longer affected leg, especially in the DCM group (23.4%, n = 30/128). A shorter affected leg was less common (17.2%, n = 22/128).

Among patients with major LLD, 59% (n = 88/149) underwent epiphysiodesis at a mean age of 11.7 years (SD ± 1.7). The highest epiphysiodesis rate was observed among

**Table 1.**

**Demographic and Clinical Characteristics of the Study Population, Stratified by Capillary Malformation Type**

| Characteristic | Total Cohort N = 1008* | RCM N = 710* | CVM N = 121* | DCM N = 128* | CM-AVM N = 49* | P value† |
|---|---|---|---|---|---|---|
| Sex | | | | | | .2 |
| Female | 557 (55.3%) | 399 (56.2%) | 68 (56.2%) | 67 (56.3%) | 20 (40.8%) | |
| Male | 451 (44.7%) | 311 (43.8%) | 53 (43.8%) | 52 (43.7%) | 29 (59.2%) | |
| Age at first encounter (years) | 1.0 (0.0–7.0) | 1.0 (0.0–6.0) | 6.0 (1.0–14.0) | 1.0 (0.0–4.0) | 5.0 (1.0–10.0) | <.001 |
| Age at last follow-up (years) | 8.0 (3.0–15.0) | 7.0 (3.0–13.0) | 16.0 (10.0–22.0) | 10.0 (4.0–15.0) | 14.0 (7.0–17.0) | <.001 |
| Duration of follow-up (years) | 4.0 (2.0–8.0) | 3.0 (2.0–6.0) | 6.0 (3.0–11.0) | 5.0 (2.0–11.0) | 4.0 (2.0–10.0) | <.001 |
| Extent of CM on the lower extremity | | | | | | <.001 |
| Partial-length-leg involvement | 786 (78.0%) | 621 (87.5%) | 89 (73.6%) | 32 (25.0%) | 44 (89.8%) | |
| Full-length-leg involvement | 222 (22.0%) | 89 (12.5%) | 32 (26.4%) | 90 (70.3%) | 5 (10.2%) | |
| Side of the body where CM is located | | | | | | <.001 |
| Left leg | 553 (54.9%) | 394 (55.5%) | 77 (63.6%) | 52 (43.7%) | 30 (61.2%) | |
| Right leg | 413 (41.0%) | 316 (44.5%) | 44 (36.4%) | 34 (28.6%) | 19 (38.8%) | |
| Both legs | 42 (4.2%) | 0 (0.0%) | 0 (0.0%) | 42 (32.8%) | 0 (0.0%) | |
| Lesion position relative to the leg midline | | | | | | |
| Medial | 244 (24.2%) | 190 (26.8%) | 21 (17.4%) | 14 (10.9%) | 19 (38.8%) | <0.001 |
| Lateral | 690 (68.5%) | 499 (70.3%) | 92 (76.0%) | 72 (56.3%) | 27 (55.1%) | <0.001 |
| Medial & lateral | 73 (7.2%) | 21 (3.0%) | 7 (5.8%) | 42 (32.8%) | 3 (6.1%) | <0.001 |
| Lesion proximity level | | | | | | <0.001 |
| 6 (hip) | 392 (38.9%) | 219 (30.8%) | 50 (41.3%) | 109 (85.2%) | 14 (28.6%) | |
| 5 (thigh) | 308 (30.6%) | 235 (33.1%) | 34 (28.1%) | 15 (11.7%) | 24 (49.0%) | |
| 4 (knee) | 47 (4.7%) | 34 (4.8%) | 11 (9.1%) | 1 (0.8%) | 1 (2.0%) | |
| 3 (lower leg) | 192 (19.0%) | 172 (24.2%) | 15 (12.4%) | 2 (1.7%) | 3 (6.1%) | |
| 2 (ankle) | 32 (3.2%) | 25 (3.5%) | 5 (4.1%) | 0 (0.0%) | 2 (4.1%) | |
| 1 (foot) | 37 (3.7%) | 25 (3.5%) | 6 (5.0%) | 0 (0.0%) | 5 (10.2%) | |
| Lesion segment count | 3.1 ± 2.3 | 2.5 ± 1.7 | 3.4 ± 1.8 | 6.6 ± 2.7 | 2.2 ± 1.5 | <.001 |
| Lesion contiguity | | | | | | <.001 |
| Single-segment | 286 (28.4%) | 246 (34.6%) | 20 (16.5%) | 0 (0.0%) | 20 (40.8%) | |
| Contiguous | 584 (57.9?%) | 377 (53.1%) | 87 (71.9%) | 99 (77.3%) | 21 (42.9%) | |
| Noncontiguous | 138 (13.7%) | 87 (12.3%) | 14 (11.6%) | 29 (22.7%) | 8 (16.3%) | |
| Presence of superficial prominent veins | 212 (21.0%) | 56 (7.9%) | 99 (81.8%) | 39 (30.5%) | 18 (36.7%) | <.001 |
| Major LLD (≥2 cm) | 149 (14.8%) | 59 (8.3%) | 25 (20.7%) | 57 (44.5%) | 8 (16.3%) | <.001 |
| Presence of any LLD at birth | 113 (11.2%) | 47 (6.6%) | 12 (9.9%) | 52 (40.6%) | 2 (4.1%) | <.001 |
| Age when LLD was first documented (months) | 13.0 (1.5–24.0) | 14.0 (6.0–27.5) | 24.0 (6.0–36.0) | 10.0 (0.0–19.5) | 10.0 (8.3–22.5) | <.001 |
| Underwent epiphysiodesis | 88 (8.7%) | 29 (4.1%) | 23 (19.0%) | 29 (22.7%) | 7 (14.6%) | <.001 |
| Age at epiphysiodesis (years) | 11.7 ± 1.7 | 11.9 ± 1.4 | 12.0 ± 1.4 | 11.0 ± 2.1 | 12.7 ± 1.1 | .01 |
| Overgrown foot of the affected leg | 323 (32.0%) | 165 (23.2%) | 53 (43.8%) | 83 (64.8%) | 22 (45.9%) | <.001 |
| Longer affected leg | 106 (10.5%) | 46 (6.5%) | 22 (18.2%) | 30 (25.2%) | 8 (16.3%) | <.001 |
| Shorter affected leg | 22 (2.2%) | 13 (1.8%) | 3 (2.5%) | 6 (5.1%) | 0 (0.0%) | <.001 |
| Thigh circumference of the affected leg | | | | | | <.001 |
| No change | 631 (62.6%) | 520 (73.2%) | 54 (44.6%) | 23 (19.3%) | 28 (58.3%) | |
| Increased | 308 (30.6%) | 149 (21.0%) | 57 (47.1%) | 79 (66.4%) | 20 (41.7%) | |
| Decreased | 69 (6.8%) | 41 (5.8%) | 10 (8.3%) | 17 (14.3%) | 0 (0.0%) | |
| Calf circumference of the affected leg | | | | | | <.001 |
| No change | 597 (59.2%) | 485 (68.3%) | 54 (44.6%) | 26 (21.8%) | 26 (54.2%) | |
| Increased | 346 (34.3%) | 185 (26.1%) | 60 (49.6%) | 76 (63.9%) | 22 (45.8%) | |
| Decreased | 65 (6.4%) | 40 (5.6%) | 7 (5.8%) | 17 (14.3%) | 0 (0.0%) | |
| Symptoms and signs on the affected leg | | | | | | |
| Leg pain | 371 (36.8%) | 199 (28.0%) | 89 (73.6%) | 50 (39.1%) | 33 (67.3%) | <.001 |
| Bleeding | 27 (2.7%) | 6 (0.8%) | 16 (13.2%) | 4 (3.1%) | 1 (2.0%) | <.001 |
| Cellulitis | 40 (4.0%) | 9 (1.3%) | 15 (12.4%) | 8 (6.3%) | 8 (16.3%) | <.001 |
| Swelling | 378 (37.5%) | 222 (31.3%) | 86 (71.1%) | 36 (28.1%) | 34 (69.4%) | <.001 |
| Ulceration | 17 (1.7%) | 5 (0.7%) | 5 (4.1%) | 4 (3.1%) | 3 (6.1%) | <.001 |
| Back pain | 45 (4.5%) | 17 (2.4%) | 13 (10.7%) | 12 (9.4%) | 3 (6.1%) | <.001 |
| Previous trauma/injury on the affected leg | 75 (7.4%) | 33 (4.6%) | 18 (14.9%) | 15 (11.7%) | 9 (18.4%) | <.001 |
| Family history of CM or LLD | 128 (12.7%) | 73 (10.3%) | 20 (16.5%) | 16 (12.5%) | 19 (38.8%) | <.001 |
| History of congenital hip dysplasia | 22 (2.2%) | 16 (2.3%) | 1 (0.8%) | 5 (4.2%) | 0 (0.0%) | .3 |

Bold *P* values indicate statistical significance.

ANOVA indicates analysis of variance; CM, capillary malformation; CM-AVM, capillary malformation-arteriovenous malformation; CVM, capillary venous malformation; DCM, diffuse capillary malformation; LLD, leg length discrepancy; RCM, Regional Capillary Malformation.

*n (%); Mean ± SD; Median (IQR).

†One-way ANOVA; Pearson's $\chi^2$ test; Kruskal-Wallis rank sum test; Fisher exact test.

the DCM group (22.7%, n = 29/128), while the lowest was in the RCM group (4.1%, n = 29/710). Of the remaining patients, 48 were still being monitored, 12 missed the surgical window due to closed growth plates, and 1 was lost to follow-up (Figure 3).

Leg pain (36.8%, n = 371) and swelling (37.5%, n = 378) were the most common symptoms reported, especially in the CVM group ($P \leq .05$). Additionally, superficial prominent veins progressively developed in 81.8% (n = 99/121) of patients with CVM.

**Table 2.**

**Univariate Logistic Regression for the Risk of Major Leg Length Discrepancy (≥2 cm)**

| Characteristic | OR | 95% CI | P value* |
|---|---|---|---|
| Sex | | | |
| Female | — | — | |
| Male | 1.01 | 0.71–1.43 | >.9 |
| Age at last follow-up (years) | 1.02 | 1.01–1.04 | <.009 |
| Age at first encounter (years) | 1.00 | 0.97–1.02 | .7 |
| Duration of follow-up | 1.10 | 1.06–1.13 | <.001 |
| CM type | | | |
| RCM | — | — | |
| CM-AVM | 2.15 | 0.90–4.58 | .061 |
| CVM | 2.87 | 1.70–4.76 | <.001 |
| DCM | 8.86 | 5.72–13.8 | <.001 |
| Extent of CM on the lower extremity | | | |
| Partial-length-leg involvement | — | — | |
| Full-length-leg involvement | 7.00 | 4.83–10.2 | <.001 |
| Side of the body where CM is located | | | |
| Left leg | — | — | |
| Right leg | 0.84 | 0.57–1.22 | .4 |
| Both legs | 6.09 | 3.17–11.7 | <.001 |
| Lesion position relative to the leg midline | | | |
| Medial | — | — | — |
| Lateral | 1.11 | 0.71–1.78 | .6 |
| Medial & lateral | 6.73 | 3.69–12.4 | <.001 |
| Lesion proximity level | 2.24 | 1.82–2.84 | <.001 |
| Lesion segment count | 1.60 | 1.48–1.75 | <.001 |
| Lesion contiguity | | | |
| Single-Segment | — | — | |
| Contiguous | 39.5 | 12.4–240 | <.001 |
| Noncontiguous | 2.41 | 6.88–152 | <.001 |
| Presence of superficial prominent veins | 3.02 | 2.08–4.38 | <.001 |
| Presence of any LLD at birth | 9.32 | 6.08–14.3 | <.001 |
| Overgrown foot of the affected leg | 10.1 | 6.79–15.4 | <.001 |
| Longer affected leg | 24.5 | 15.5–40.4 | <.001 |
| Shorter affected leg | 3.15 | 1.82–5.32 | <.001 |
| Calf circumference of the affected leg | | | |
| No change | — | — | |
| Increased | 13.1 | 8.21–22.0 | <.001 |
| Decreased | 8.96 | 4.34–18.2 | <.001 |
| Thigh circumference of the affected leg | | | |
| No change | — | — | |
| Increased | 14.1 | 8.88–23.2 | <.001 |
| Decreased | 10.0 | 5.09–19.7 | <.001 |
| Symptoms of the affected leg | | | |
| Leg pain | 1.75 | 1.23–2.49 | <.009 |
| Bleeding | 3.00 | 1.26–6.66 | .009 |
| Cellulitis | 3.31 | 1.65–6.43 | <.001 |
| Swelling | 0.85 | 0.58–1.21 | .4 |
| Ulceration | 3.23 | 1.10–8.64 | .02 |
| Previous trauma/ Injury on the affected leg | 8.64 | 5.27–14.2 | <.001 |
| Family history of CM or LLD | 0.87 | 0.49–1.46 | .6 |
| History of congenital hip dysplasia | 7.44 | 3.15–17.9 | <.001 |

Bold *P* values indicate statistical significance.

CI indicates confidence interval; CM, capillary malformation; CM-AVM, capillary malformation-arteriovenous malformation; CVM, capillary venous malformation; DCM, diffuse capillary malformation; LLD, leg length discrepancy; OR, odds ratio; RCM, Regional Capillary Malformation.

*Wald test.

### *Regression analysis*

Univariate logistic regression identified several predictors of significant LLD (Table 2). Older age at last follow-up and longer follow-up periods were associated with higher risks of LLD (odds ratio [OR], 1.02 per year; 95% CI, 1.01–1.04; *P* < .009; OR, 1.10 per year; 95% CI, 1.06–1.13; *P* < .001, respectively). The presence of CVM and DCM was associated with higher odds of LLD, with ORs of 2.87 (95% CI, 1.70–4.76; *P* < .001) and 8.86 (95% CI, 5.72–13.8, *P* < .001), respectively. Patients with lesions on both legs were linked to a 6-fold higher risk (OR, 6.09; 95% CI, 3.17–11.7; *P* < .001), and full-length leg involvement was associated with a higher likelihood of developing a major LLD (OR, 7.00; 95% CI, 4.83–10.2; *P* < .001). The positioning of CM lesions, especially when combined medially and laterally, was associated with a significant increase in LLD risk (OR, 6.73; 95% CI, 3.69–12.4; *P* < .001) compared to isolated medial or lateral lesions. A greater number of affected leg segments by a CM lesion significantly correlated with a higher risk of major LLD (OR, 1.60; 95% CI, 1.48–1.75; *P* < .001). Compared with single-segment lesions (reference), contiguous lesions had an OR of 39.5 (95% CI, 12.4–240; *P* < .001), and noncontiguous lesions had an OR of 2.41 (95% CI, 6.88–152; *P* < .001). Developing a longer affected leg was linked with substantially higher odds of major LLD (OR, 24.5; 95% CI, 15.5–40.4; *P* < .001) compared to a

**Table 3.**

**Multivariate Logistic Regression for the Risk of Major Leg Length Discrepancy (≥2 cm)**

| Characteristic | OR | 95% CI | P value* |
|---|---|---|---|
| Age at encounter (years) | 0.99 | 0.97–1.02 | .6 |
| Sex | | | |
| Female | — | — | |
| Male | 0.90 | 0.58–1.40 | .6 |
| CM type | | | |
| RCM | — | — | |
| CM-AVM | 1.37 | 0.30–5.28 | .7 |
| CVM | 2.09 | 0.66–6.62 | .2 |
| DCM | 4.65 | 1.57–14.3 | .01 |
| Extent of CM on the lower extremity | | | |
| Partial-length-leg involvement | — | — | |
| Full-length-leg involvement | 1.46 | 0.86–2.47 | .2 |
| Side of the body where CM is located | | | |
| Left leg | — | — | |
| Right leg | 0.73 | 0.45–1.17 | .2 |
| Both legs | 0.88 | 0.35–2.18 | .8 |
| Lesion position relative to the leg midline | | | |
| Medial | — | — | |
| Lateral | 0.69 | 0.40–1.20 | .2 |
| Medial & Lateral | 1.56 | 0.71–3.45 | .3 |
| Lesion proximity level | 1.40 | 1.09–1.83 | .01 |
| Lesion segment count | 1.35 | 1.10–1.67 | .005 |
| Lesion contiguity | | | |
| Single-segment | — | — | |
| Contiguous | 16.9 | 5.23–103 | <.001 |
| Noncontiguous | 6.45 | 1.46–44.5 | .02 |
| Presence of superficial prominent veins | 1.47 | 0.84–2.57 | .2 |
| Overgrown foot of the affected leg | 4.95 | 2.66–9.47 | <.001 |
| Calf circumference of the affected leg | | | |
| No change | — | — | |
| Increased | 2.44 | 1.18–5.16 | .02 |
| Decreased | 0.29 | 0.05–1.68 | .2 |
| Thigh circumference of the affected leg | | | |
| No change | — | — | |
| Increased | 2.08 | 1.03–4.22 | .04 |
| Decreased | 28.3 | 5.02–152 | <.001 |
| Family history of CM or LLD | 0.63 | 0.32–1.20 | .2 |
| History of congenital hip dysplasia | 7.75 | 2. –25.7 | <.001 |

Hosmer and Lemeshow goodness of fit (GOF) test: *P* value = .33; AIC: 578.1.

Bold *P* values indicate statistical significance.

CI indicates confidence interval; CM, capillary malformation; CM-AVM, capillary malformation-arteriovenous malformation; CVM, capillary venous malformation; DCM, diffuse capillary malformation; LLD, leg length discrepancy; OR, odds ratio; RCM, Regional Capillary Malformation.

*Wald test.

shorter affected leg (OR, 3.15; 95% CI, 1.82–5.32; *P* < .001). Furthermore, the appearance of superficial prominent veins, prior trauma or injury on the affected leg, and history of congenital hip dysplasia were all associated with a higher likelihood of major LLD, with ORs of 3.02, 8.64, and 7.44, respectively (*P* < .001).

Ordinal logistic regression indicated that each unit increase in lesion proximity level was associated with more than a 3-fold increase in the likelihood of developing major LLD (OR, 3.55; 95% CI, 2.17–5.82; *P* < .001). Conversely, the risk of developing an overgrown foot on the affected leg decreased by 28% for each unit increase in proximity level (OR, 0.72; 95% CI, 0.53–0.98; *P* = .03). Proximally located lesions were linked to a higher likelihood of major LLD by age 15, whereas distally located lesions were more likely to result in an overgrown foot rather than LLD.

Adjusted logistic regression analysis (Table 3) showed that the DCM subtype was associated with a significantly higher risk of major LLD (OR, 4.65; 95% CI, 1.57–14.3; *P* = .01). Each additional affected area by the CM was associated with a 35% increase in the risk of major LLD (OR, 1.35; 95% CI, 1.10–1.67; *P* = .005). Compared with single-segment lesions (reference), contiguous lesions had an adjusted OR of 16.9 (95% CI, 5.23–103; *P* < .001), and noncontiguous lesions had an adjusted OR of 6.45 (95% CI, 1.46–44.5; *P* = .02). Each unit increase in lesion proximity was associated with a 40% higher risk of LLD (OR, 1.40; 95% CI, 1.09–1.83; *P* = .01). The development of an overgrown foot was linked to nearly 5-fold higher odds of major LLD (OR, 4.95; 95% CI, 2.66–9.47; *P* < .001). A history of congenital hip dysplasia was also associated with a higher risk (OR, 7.75; 95% CI, 2.00–25.7; *P* < .001). The model's adequacy was confirmed by the Hosmer and Lemeshow test (*P* = .33), and the receiver operating characteristic curve indicated robust predictive performance (area under the curve, 0.9), though not cross-validated.

### *Survival analysis*

The Kaplan–Meier survival analysis estimated a 31.4% cumulative risk of developing a major LLD (≥2 cm) by age 15 in children with lower extremity CM (standard error [SE], 2.21%; 95% CI, 27.32–35.98%), accommodating variable follow-up durations and right-censoring

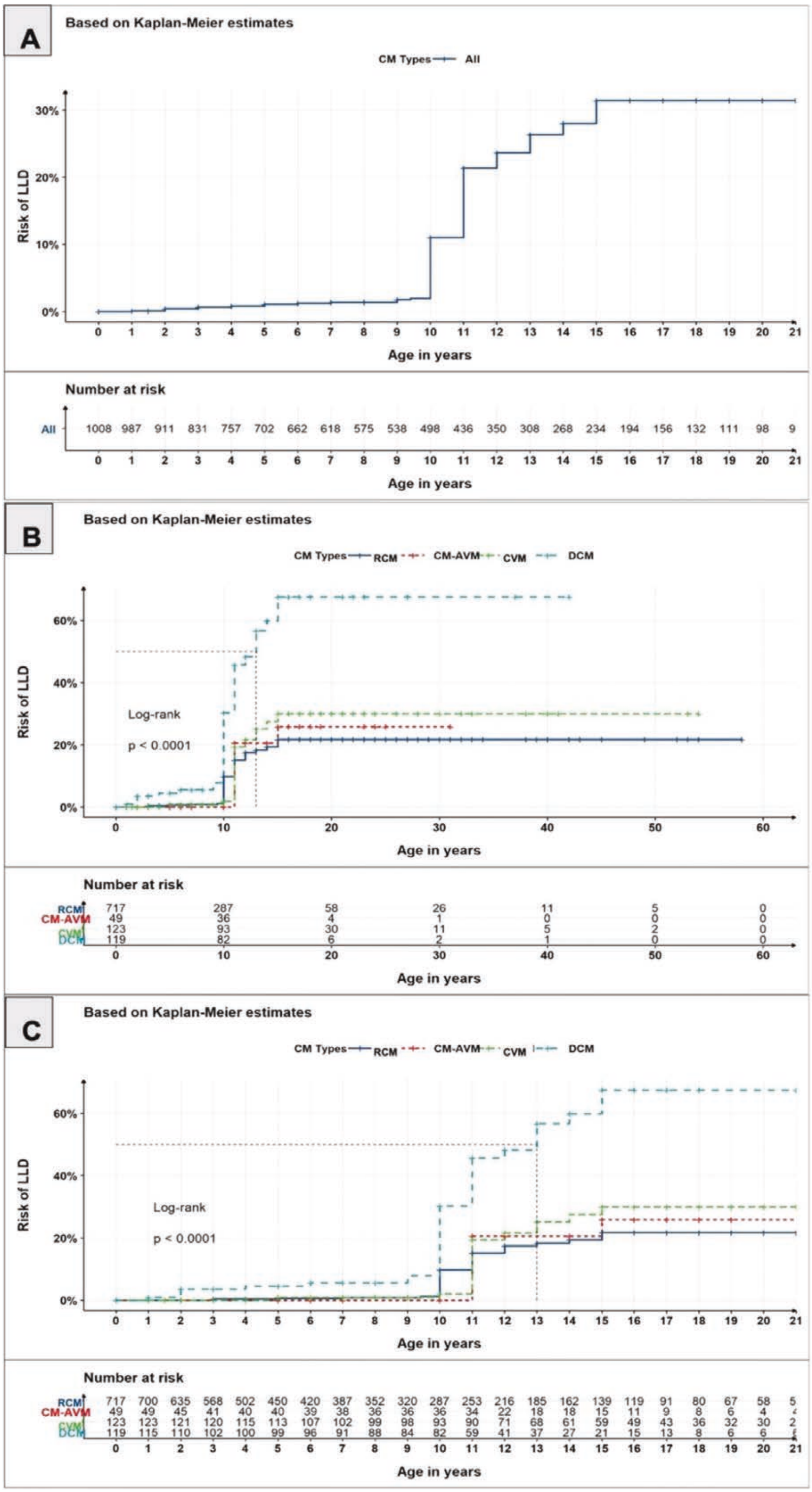



**Figure 4.** Cumulative probability of major LLD development in children with leg CM: A, Overall likelihood of LLD development by age. B, Risk estimates by CM subtype. C, Time stratified LLD risk for each CM subtype. CM, capillary malformation; CM-AVM, capillary malformation-arteriovenous malformation; CVM, capillary venous malformation; DCM, diffuse capillary malformation; LLD, leg length discrepancy; RCM, regional capillary malformation.

(Figure 4A). Estimates near the upper age range should be interpreted with caution due to smaller numbers at risk. The stratified analysis indicated increasing LLD risk across CM subtypes: RCM at risk of 21.88% (SE, 2.61%; 95% risk CI, 16.60–26.83%), CM-AVM at 25.88% (SE, 0.82%; 95% risk CI, 7.82–40.41%), CVM at 28.48% (SE, 4.85%; 95% risk CI, 18.31–37.38%), and DCM with the highest at 66.4% (SE, 5.50%; 95% risk CI, 53.70–75.60%) (Figure 4B,C).

Figure 4 shows a clear inflection in the Kaplan–Meier curves beginning around age 10–12 years, at which point the proportion of patients crossing the ≥2 cm threshold for lower-limb discrepancy rises more sharply.

### *Genetic analysis*

Genetic testing was performed on 5.8% of patients (n = 59), predominantly those with CM-AVM (37.3%, n = 22/59) (*P* < .001) (Table 4). No mutations were identified in 19/59 cases (32.2%). The most commonly identified genetic mutations were of *RASA-1* (23.7%, n = 14/59) and *PIK3CA* (20.3%, n = 12/59). There was no significant association between genetic mutation and LLD on regression analysis. However, *PIK3CA* mutations showed a borderline significant relationship with major LLD (OR, 4.90; 95% CI, 1.04–26.8; *P* =.05).

## Discussion

Our study highlights the significant impact of the CM on the lower extremity, with 14.8% of affected children developing a clinically meaningful LLD of 2 cm or more, compared with the background LLD rates of 4.8–7% in the general pediatric population.[20,21] Additionally, we found that children with lower extremity CM had a 31.4% risk of progressing to major LLD by age 15.

Aside from the 11.2% of patients who presented with an LLD at birth, the majority of patients had their initial discrepancy documented by age 2, with a median detection age of 13 months (IQR, 1.5–24 months), indicating that significant discrepancies (major LLD) can manifest early (by age 2) and may accelerate near the pubertal growth spurt. Accordingly, in our practice, we begin clinical assessments for LLD starting at 1 year of age to support early detection and follow-up planning. The frequency of follow-up and any imaging studies is determined on a case-by-case basis, guided by each child's clinical status and the degree of discrepancy.

Identifying high-risk patients may facilitate earlier identification of LLD so that they do not miss the opportunity for epiphysiodesis and subsequently risk LLD-related complications. In general, the growth plates in the lower extremity begin to close around ages 14–18 for girls and 16–20 for boys, with the peak growth spurt occurring in early to mid-adolescence. In our Kaplan–Meier analysis (Figure 4), we observed an inflection point around age 10–12, which likely corresponds to the onset of the pubertal growth spurt; even minimal discrepancies can rapidly exceed the ≥2 cm threshold at this stage. Recognizing this period is critical for timely orthopedic assessment, as epiphysiodesis is most effective before physeal closure. In our cohort, 12 patients with major LLD missed the window for epiphysiodesis due to growth plate closure. Although surgical options are available for patients with major LLD at skeletal maturity (femoral shortening of the longer limb or lengthening of the shorter limb), such procedures are more invasive, require longer recovery periods, and carry higher complication

**Table 4.**

**Descriptive Statistics and Logistic Regression Analysis of Genetic Testing Outcomes, Stratified by CM Type in the Study Population**

| Characteristic | Total Cohort N=1008* | RCM N = 710* | CVM N = 121* | DCM N = 128* | CM-AVM N = 49* | P value† | OR | 95% CI | P value‡ |
|---|---|---|---|---|---|---|---|---|---|
| Genetic testing performed | 59 (5.8%) | 16 (2.2%) | 6 (4.9%) | 15 (11.7%) | 22 (44.9%) | <.001 | | | |
| Tissue used for genetic testing | | | | | | .003 | | | |
| Not disclosed | 16 (27.1%) | 3 (18.7%) | 2 (33.3%) | 4 (25.0%) | 7 (33.3%) | | 0.83 | 0.15–4.02 | .8 |
| Blood sample | 24 (40.7%) | 7 (43.7%) | 0 (0.0%) | 4 (25.0%) | 13 (61.9%) | | — | — | |
| Skin biopsy | 4 (6.8%) | 1 (6.2%) | 0 (0.0%) | 3 (18.8%) | 0 (0.0%) | | 3.60 | 0.36–37.1 | .3 |
| Buccal swab | 3 (5.1%) | 2 (12.6%) | 0 (0.0%) | 0 (0.0%) | 1 (4.8%) | | 1.80 | 0.07–23.0 | .7 |
| Tissue biopsy | 12 (20.3%) | 3 (18.8%) | 4 (66.7%) | 5 (31.3%) | 0 (0.0%) | | 7.20 | 1.62–38.1 | .01 |
| Mutated gene | | | | | | <.001 | | | |
| No mutation detected | 19 (32.2%) | 6 (37.5%) | 1 (16.7%) | 6 (40.0%) | 6 (27.3%) | | — | — | |
| *RASA-1* | 14 (23.7%) | 1 (6.2%) | 0 (0.0%) | 0 (0.0%) | 13 (59.1%) | | 0.22 | 0.01–1.57 | .2 |
| *PIK3CA* | 12 (20.3%) | 2 (12.5%) | 3 (50.0%) | 7 (46.6%) | 0 (0.0%) | | 4.90 | 1.04–26.8 | .05 |
| *EPHB4* | 2 (3.4%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 2 (9.1%) | | 0.00 | | >.9 |
| *KRAS* | 2 (3.4%) | 2 (12.5%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | | 2.80 | 0.10–80.6 | .5 |
| *PIK3R1* | 2 (3.4%) | 1 (6.2%) | 0 (0.0%) | 1 (6.7%) | 0 (0.0%) | | 2.80 | 0.10–80.6 | .5 |
| *CHD4, PDGFRB* | 1 (1.7%) | 0 (0.0%) | 0 (0.0%) | 1 (6.7%) | 0 (0.0%) | | | 0.00–NA | >.9 |
| *GNA11* | 1 (1.7%) | 1 (6.2%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | | | 0.00–NA | >.9 |
| *GNAQ* | 1 (1.7%) | 0 (0.0%) | 1 (16.7%) | 0 (0.0%) | 0 (0.0%) | | 0.00 | | >.9 |
| *IDH1* | 1 (1.7%) | 0 (0.0%) | 1 (16.7%) | 0 (0.0%) | 0 (0.0%) | | | 0.00–NA | >.9 |
| *MTOR* | 1 (1.7%) | 1 (6.2%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | | | 0.00–NA | >.9 |
| *NLGN4X* | 1 (1.7%) | 1 (6.2%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | | 0.00 | | >.9 |
| *MAP2K1* | 1 (1.7%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 1 (4.5%) | | 0.00 | | >.9 |
| *YAP1* | 1 (1.7%) | 1 (6.2%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | | 0.00 | | >.9 |
| Mutation variant | | | | | | <.001 | | | |
| Not available | 33 (55.9%) | 12 (75.0%) | 3 (50.0%) | 12 (80.0%) | 6 (27.3%) | | — | — | |
| Germline | 18 (30.5%) | 2 (12.5%) | 0 (0.0%) | 0 (0.0%) | 16 (72.7%) | | 0.13 | 0.01–0.76 | .06 |
| Somatic | 2 (3.4%) | 1 (6.25%) | 0 (0.0%) | 1 (6.7%) | 0 (0.0%) | | 1.91 | 0.07–51.5 | .7 |
| Tissue specific | 6 (10.2%) | 1 (6.25%) | 3 (50.0%) | 2 (13.3%) | 0 (0.0%) | | | 0.00–NA | >.9 |

Bold *P* values indicate statistical significance and borderline significance.

ANOVA indicates analysis of variance; CI, confidence interval; CM, capillary malformation; CM-AVM, capillary malformation-arteriovenous malformation; CVM, capillary venous malformation; DCM, diffuse capillary malformation; LLD, leg length discrepancy; OR, odds ratio; RCM, Regional Capillary Malformation.

*n (%); mean ± SD; median (IQR).

†One-way ANOVA; Pearson's $\chi^2$ test; Kruskal-Wallis rank sum test; Fisher exact test.

‡Wald test.

rates compared with epiphysiodesis.[22] Therefore, we recommend that children with lower extremity CM receive their first orthopedic evaluation around 12 months of age. If no discrepancy is detected, routine follow-up around age 4 is appropriate; however, surveillance should increase as they approach puberty, when minimal discrepancies may rapidly exceed the ≥2 cm threshold. This schedule helps ensure timely consideration of epiphysiodesis before physeal closure.

We identified CM subtype and extent as key clinical predictors for developing major LLD. Among the CM subtypes, DCM posed the highest risk, with 66.4% of DCM patients expected to develop major LLD by age 15. Given their high-risk status and established association with both overgrowth[23–25] and undergrowth,[26] children with DCM should be particularly closely monitored for LLD.

In terms of CM extent and size, we found that full-length leg involvement, combined medial and lateral involvement, bilateral leg involvement, and each additional affected area by the CM significantly increased the risk of LLD. The risk associated with full-length leg involvement is supported by a previous analysis of 361 patients with lower extremity vascular anomalies.[4] Furthermore, we identified that more proximal CM distribution increased the risk of major LLD. We hypothesize that more extensive and/or more proximally distributed CMs may reflect a somatic mutation or a "second-hit" mutation in CM-AVM[27] occurring at an earlier developmental stage. Earlier mutations may involve a greater degree of cutaneous tissue and are more likely to affect additional structures such as bone and soft tissue, potentially spanning multiple growth plates and influencing leg length.[28,29] Involvement of proximal structures, such as the pelvis and thigh, had a greater influence on leg length than small distal bones of the ankle and foot. Alternatively, perhaps the level of increased blood flow within more extensive lesions affects the degree of hypertrophy. Understanding how the distribution, location, and extent of a CM lesion influence the risk of LLD can help guide risk stratification for individual patients. Future prospective studies could incorporate standardized methods for quantifying body surface area involvement, similar to burn nomograms, to more precisely correlate CM extent with LLD risk.

Children with a history of hip dysplasia had an almost 8-fold higher risk of developing major LLD, consistent with the existing literature that recognizes congenital hip dysplasia as a critical risk factor due to altered hip joint development and mechanical imbalances.[18,30] Hip dysplasia, in combination with a CM, may exacerbate asymmetrical growth patterns, potentially augmenting the risk of LLD. Early orthopedic assessment is essential to manage the compounded risk in this specific population.

A small proportion of patients (5.8%) in our cohort underwent genetic testing. Many patients in this study were seen prior to genetic testing being readily available. Mutations of *RASA-1* were the most commonly identified genetic change (14/59, 23.7%). Genetic testing was frequently performed in patients suspected of CM-AVM, given that an identified mutation of *RASA-1* or *EPHB4* may change management (MRI screening of the brain and spine[31]). Although the option of genetic testing is often discussed, many patients with CM subtypes other than CM-AVM choose to defer. Testing for somatic mutations also requires a skin biopsy, compared with a cheek swab or blood draw for germline genetic testing in CM-AVM.

Mutations in *PIK3CA* were the second most commonly identified (20.3%, n = 12/59) and displayed a borderline significant association with LLD (*P* = .051). Given the established role of somatic activating *PIK3CA* mutations in overgrowth syndromes, this possible association is worth further investigation in future studies with larger sample sizes.[23,25,26,28,29,32–34] The few identified mutations in genes such as *KRAS*, *GNA11*, *GNAQ*, *MAPK21*, *MTOR*, and *PIK3R1* reflect the heterogeneity of CM pathogenesis.[19,23,25,28,32,33] Although many of these genes and pathways play established roles in the development of vascular anomalies, nearly a third of our patients who underwent genetic testing (32.2%, n = 19/59) had no mutation identified. This highlights how much there is still to be learned about the mechanisms of CM formation. Furthermore, in tandem with the heterogeneity of mutations involved, the timing of a postzygotic mutation (or second-hit as above) in embryogenesis and the subsequent extent of tissue type(s) involved in the malformation likely plays a critical role in the pathogenesis of an associated condition such as LLD.

Limitations of this study are typical of single-center retrospective designs and include the inability to establish causation, residual confounding, potential selection bias from excluding cases with incomplete data, and limited generalizability of our findings. Additionally, using radiographic and physical examinations to confirm LLD could lead to measurement bias due to inter-practitioner variation. Patients referred to our vascular anomalies center may skew towards more severe cases, potentially leading to an overestimation of LLD rates. The final predictive model was not internally validated (eg, bootstrapping or cross-validation), which may overestimate performance despite an acceptable events-per-variable ratio. As only a small portion of our patients underwent genetic testing, further investigation into the genetics of CM is warranted. Although Kaplan–Meier modeling accounts for censoring in retrospective cohorts, risk estimates near age 15 should be interpreted cautiously due to fewer patients remaining under observation and varying follow-up lengths. A prospective, multicenter registry approach, potentially standardizing structured data collection (eg, LLD measurements at regular intervals), would enable more robust modeling of LLD progression and confirm our results across diverse patient populations. Future steps should also include internal validation using bootstrapping and external validation in an independent or multicenter cohort to assess generalizability and support the model's potential use in clinical risk prediction.

## Conclusion

This study reveals a significant association between lower extremity CM and lower-limb length discrepancies, with 14.8% of affected children developing clinically meaningful discrepancies. By age 15, the overall progressive risk of developing major LLD is 31.4% across all cases, escalating to 66.4% among patients with DCM. Significant LLD predictors include the DCM subtype, larger affected areas, proximal lesion location, full-length leg involvement, and combined medial and lateral leg involvement. Genetic risk factors are not currently well understood and require further investigation. Overall, we advocate for early and close clinical monitoring for LLD in children with lower extremity CM to facilitate timely intervention and reduce long-term complications.

## Acknowledgments

We sincerely thank Dr. John B. Mulliken, from the Vascular Anomalies Center and the Department of Plastic and Oral Surgery at Boston Children's Hospital and Harvard Medical School (Boston, MA, United States), for his exceptional mentorship, clinical insight, and foundational contributions to the field that guided this work.

## References

1. Jacobs AH, Walton RG. The incidence of birthmarks in the neonate. *Pediatrics*. 1976;58:218–222.
2. Rozas-Muñoz E, Frieden IJ, Roé E, Puig L, Baselga E. Vascular stains: proposal for a clinical classification to improve diagnosis and management. *Pediatr Dermatol*. 2016;33:570–584.
3. Enjolras O, Chapot R, Jacques Merland J. Vascular anomalies and the growth of limbs: a review. *J Pediatr Orthop B*. 2004;13:349–357.
4. Kim Y-W, Lee S-H, Kim D-I, Do Y-S, Lee B-B. Risk factors for leg length discrepancy in patients with congenital vascular malformation. *J Vasc Surg*. 2006;44:545–553.
5. Spencer SA, Sorger JI. Orthopedic issues in vascular anomalies. *Semin Pediatr Surg*. 2020;29:150973.
6. Vitale MA, Choe JC, Sesko AM, et al. The effect of limb length discrepancy on health-related quality of life: is the "2 cm rule" appropriate? *J Pediatr Orthop B*. 2006;15:1–5.
7. Murray KJ, Azari MF. Leg length discrepancy and osteoarthritis in the knee, hip and lumbar spine. *J Can Chiropr Assoc*. 2015;59:226–237.
8. Rannisto S, Okuloff A, Uitti J, et al. Leg-length discrepancy is associated with low back pain among those who must stand while working. *BMC Musculoskelet Disord*. 2015;16:110.
9. Khamis S, Carmeli E. Relationship and significance of gait deviations associated with limb length discrepancy: a systematic review. *Gait Posture*. 2017;57:115–123.
10. Guichet JM, Spivak JM, Trouilloud P, Grammont PM. Lower limb-length discrepancy. An epidemiologic study. *Clin Orthop Relat Res*. 1991:235–241.
11. Makarov MR, Dunn SH, Singer DE, et al. Complications associated with epiphysiodesis for management of leg length discrepancy. *J Pediatr Orthop*. 2018;38:370–374.
12. Gordon JE, Davis LE. Leg length discrepancy: the natural history (and what do we really know). *J Pediatr Orthop*. 2019;39:S10–S13.
13. Song KM, Halliday SE, Little DG. The effect of limb-length discrepancy on gait*. *J Bone Joint Surg Am*. 1997;79:1690–1698.
14. Mishima K, Kitoh H, Kadono I, et al. Prediction of clinically significant leg-length discrepancy in congenital disorders. *Orthopedics*. 2015;38:e919–e924.
15. ISSVA classification for vascular anomalies. International Society for the Study of Vascular Anomalies; 2018 website, https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf. Accessed May 24, 2025.
16. Benjamini Y, Drai D, Elmer G, Kafkafi N, Golani I. Controlling the false discovery rate in behavior genetics research. *Behav Brain Res*. 2001;125:279–284.
17. Althouse AD. Adjust for multiple comparisons? It's not that simple. *Ann Thorac Surg*. 2016;101:1644–1645.
18. Yoon C, Shin CH, Kim DO, et al. Overgrowth of the lower limb after treatment of developmental dysplasia of the hip: incidence and risk factors in 101 children with a mean follow-up of 15 years. *Acta Orthop*. 2020;91:197–202.
19. Canaud G, Hammill AM, Adams D, Vikkula M, Keppler-Noreuil KM. A review of mechanisms of disease across PIK3CA-related disorders with vascular manifestations. *Orphanet J Rare Dis*. 2021;16:306.
20. Drnach M, Kreger A, Corliss C, Kocher D. Limb length discrepancies among 8- to 12-year-old children who are developing typically. *Pediatr Phys Ther*. 2012;24:334–337.
21. Nissinen M, Heliövaara M, Tallroth K, Poussa M. Trunk asymmetry and scoliosis anthropometric measurements in prepuberal school children. *Acta Paediatr Scand*. 1989;78:747–753.
22. Tan F, Yang C, Zeng J, et al. A systematic review and meta-analysis: comparing the efficacy of the Ilizarov technique alone with lengthening over a nail for lower extremity bone defects. *BMC Musculoskelet Disord*. 2024;25:699.
23. Goss JA, Konczyk DJ, Smits P, et al. Diffuse capillary malformation with overgrowth contains somatic PIK3CA variants. *Clin Genet*. 2020;97:736–740.
24. Liu KX, Prajapati VH, Liang MG, Mulliken JB, Lee MS. A cross-sectional survey of long-term outcomes for patients with diffuse capillary malformation with overgrowth. *J Am Acad Dermatol*. 2018;78:1023–1025.
25. Lee MS, Liang MG, Mulliken JB. Diffuse capillary malformation with overgrowth: a clinical subtype of vascular anomalies with hypertrophy. *J Am Acad Dermatol*. 2013;69:589–594.
26. Cubiró X, Rozas-Muñoz E, Castel P, et al. Clinical and genetic evaluation of six children with diffuse capillary malformation and undergrowth. *Pediatr Dermatol*. 2020;37:833–838.
27. Macmurdo CF, Wooderchak-Donahue W, Bayrak-Toydemir P, et al. RASA1 somatic mutation and variable expressivity in capillary malformation/arteriovenous malformation (CM/AVM) syndrome. *Am J Med Genet A*. 2016;170:1450–1454.
28. Couto JA, Ayturk UM, Konczyk DJ, et al. A somatic GNA11 mutation is associated with extremity capillary malformation and overgrowth. *Angiogenesis*. 2017;20:303–306.
29. Lee K, Park JE, Eom Y, Lim HS, Ki C, Lim SY. Phenotypic association of presence of a somatic GNAQ mutation with port-wine stain distribution in capillary malformation. *Head Neck*. 2019;41:4143–4150.
30. Tolk JJ, Merchant R, Eastwood DM, Buddhdev P, Hashemi-Nejad A. The development of leg length difference and influence on persistent dysplasia in patients with developmental dysplasia of the hip. *Indian J Orthop*. 2021;55:1568–1575.
31. Thiex R, Mulliken JB, Revencu N, et al. A novel association between RASA1 mutations and spinal arteriovenous anomalies. *AJNR Am J Neuroradiol*. 2010;31:775–779.
32. Couto JA, Huang L, Vivero MP, et al. Endothelial cells from capillary malformations are enriched for somatic GNAQ mutations. *Plast Reconstr Surg*. 2016;137:77e–82e.
33. Bichsel C, Bischoff J. A somatic missense mutation in GNAQ causes capillary malformation. *Curr Opin Hematol*. 2019;26:179–184.
34. Keppler-Noreuil KM, Rios JJ, Parker VER, et al. PIK3CA -related overgrowth spectrum (PROS): diagnostic and testing eligibility criteria, differential diagnosis, and evaluation. *Am J Med Genet A*. 2015;167:287–295.