North Clin Istanb 2026;13(5):513–522
doi: 10.14744/nci.2026.64928

Original Article PM & R

Is there a relationship between joint hypermobility and primary lymphedema? A cross-sectional study

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ABSTRACT

OBJECTIVE: This study aimed to evaluate the association between joint hypermobility (JH) and primary lymphedema.

METHODS: This cross-sectional study included 36 patients (30 females and 6 males; age range, 18–65 years) diagnosed with primary lower extremity lymphedema and 32 age-matched healthy controls. Demographic characteristics were recorded for all participants. Generalized joint hypermobility (GJH) was assessed using the Beighton scoring system, and Benign joint hypermobility syndrome (BJHS) was evaluated according to the Brighton criteria.

RESULTS: GJH was observed in 27.8% of patients with lymphedema and 25% of controls, with no statistically significant difference between groups ($p>0.05$). Similarly, the frequency of BJHS was comparable between the lymphedema group (13.9%) and the control group (15.6%; $p>0.05$). Mean Beighton scores did not differ significantly between the lymphedema and control groups ($p>0.05$). Furthermore, neither Beighton scores nor the prevalence of BJHS differed significantly across lymphedema stages ($p>0.05$).

CONCLUSION: JH was not significantly associated with primary lymphedema. Our study may provide a foundation for future research aiming to clarify the relationship between JH and primary lymphedema through objective diagnostic criteria and quantitative connective tissue assessments.

Keywords: Connective tissue; joint hypermobility; lymphedema.

Cite this article as: *Begoglu FA, Ozturk G, Kaysin MY, Karamanlioglu AD, Ozkan FU, Aktas I. Is there a relationship between joint hypermobility and primary lymphedema? A cross-sectional study. North Clin Istanb 2026;13(5):513–522.*

Joint hypermobility (JH) is a clinical condition defined by an excessive range of motion in one or more joints beyond normal physiological limits [1]. The reported prevalence of JH varies widely, ranging from 0.6% to 31.5%, depending on demographic factors such as race, age, and sex. It is more prevalent in women than in men and shows a progressive decline with advancing age [2, 3]. Involvement of multiple joints is generally referred to as generalized joint hypermobility (GJH) or joint laxity [4–6]. JH represents a spectrum ranging from asymptomatic benign hypermobility to symptomatic hypermobility disorders. The Beighton Scoring System – a widely used 9-point scale for assessing articular hypermobility in adults – has been incorporated into both prior and current diagnostic criteria for hypermobility syndromes [7–11]. Despite its recognized limitations [8, 9], the scale remains the most widely accepted assessment tool, with a Beighton score of ≥4 commonly applied as the threshold for defining GJH [12–14].

Received: May 06, 2026 *Revised:* July 29, 2026 *Accepted:* August 06, 2026 *Online:* October 15, 2026

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Istanbul Provincial Directorate of Health - Available online at www.northclinist.com

GJH is widely recognized as a hallmark feature of various hereditary connective tissue disorders; however, its underlying pathophysiological mechanisms remain poorly understood [4, 15]. It has been associated with structural abnormalities in mesoderm-derived connective tissues, particularly muscle, tendon, and venous vascular structures [3, 16–18]. In individuals with JH, alterations in collagen composition, especially an increased ratio of type III to type I collagen, have been documented. These abnormalities in collagen structure contribute to joint laxity and increased fragility of connective tissue [1, 19].

In the last decade, growing attention has been directed toward JH and its related disorders. The literature abounds with case–control studies demonstrating a significant association between GJH – commonly assessed using the Beighton score – and specific extra-articular manifestations [4, 6, 12–15]. In 2017, Castori et al. [4] defined JH and these associated complications as JH-related comorbidities, among which cardiovascular manifestations represent a notable component [15]. JH is associated with venous disorders to varying degrees. Laxity of the vessel walls in patients with underlying connective tissue abnormalities may explain this association [18, 20]. Fundamentally, the lymphatic and venous systems predominantly arise from a shared mesodermal lineage [21–23]. The lymphatic system depends on connective tissue both for structural support and for the proper functioning of its anchoring filament network [24]. Impairment of lymphatic transport capacity leads to interstitial fluid accumulation, triggering progressive remodeling of fibro-adipose connective tissue [25, 26]. Primary lymphedema may occur either as an isolated disorder or as a component of complex genetic syndromes that include vascular anomalies [27, 28].

GJH has not yet been systematically evaluated in patients with primary lymphedema, a disorder of the lymphatic system that shares a common developmental origin with connective tissue. Given the gaps in the current literature and the potential clinical implications of establishing a link between primary lymphedema and hypermobility, the present study aimed to examine the association between GJH and primary lymphedema and to explore its relationship with lymphedema stages.

Highlight key points

- JH was identified in 27.8% of patients with primary lymphedema but showed no significant association with either the presence or severity of lymphedema.
- Age was inversely associated with GJH, consistent with the well-documented decline in JH with advancing age.
- These findings may establish a reference point for future research incorporating objective diagnostic criteria and quantitative connective tissue assessments to further clarify the relationship between JH and primary lymphedema.

MATERIALS AND METHODS

This cross-sectional observational study included 36 patients aged 18–65 years who presented to the Physical Medicine and Rehabilitation (PMR) lymphedema outpatient clinic with lower-extremity swelling and were diagnosed with primary lymphedema, as well as 32 age-matched healthy volunteers. Participants were enrolled between April and October 2024.

All patients were evaluated by an experienced PMR specialist. The diagnosis of primary lymphedema was established in accordance with the diagnostic approach outlined in the 2023 Consensus Document of the International Society of Lymphology [25], based on a combination of medical history and physical examination findings. Diagnostic criteria included lower-extremity swelling, a positive Stemmer sign, the presence or absence of pitting edema, normal Doppler ultrasonography findings, and normal abdominopelvic and inguinal ultrasonography for etiological assessment. Lymphatic insufficiency was defined by lymphoscintigraphic findings, including delayed tracer transit time, dermal backflow, asymmetric nodal uptake, the presence of collateral lymphatic channels, and tracer uptake in the deep lymph nodes [29].

Patients diagnosed with primary lymphedema were classified according to disease severity as Stage I, II, or III. Stage I was defined by pitting edema that improved with limb elevation; Stage II by persistent pitting edema unresponsive to elevation; and Stage III by fibro-adipose tissue deposition accompanied by skin changes [25]. Age-matched healthy volunteers were recruited as controls. Healthy controls were selected from volunteers without a history or clinical signs of lymphedema, lower-extremity edema, connective tissue disorder, or any known musculoskeletal or neurological condition that could affect joint mobility. All controls underwent the same clinical assessment procedure for JH as the lymphedema group.

Exclusion criteria included secondary lymphedema; lower-extremity edema due to cardiac, renal, hepatic, or myxedematous causes; use of medications known to cause edema (including corticosteroids, calcium chan-

nel blockers, gabapentin, and pregabalin); a diagnosis of rheumatologic disease; and the presence of active cellulitis or erysipelas of the lower extremities in patients with primary lymphedema.

Demographic data were recorded for all participants. Joint range of motion was assessed during the evaluation visit using the Beighton scoring system, and the Brighton criteria were applied. Age-dependent cutoff scores of ≥5 for individuals aged 18–50 years and ≥4 for individuals aged >50 years were used in the current study, according to the 2017 updated criteria for the Beighton score [11, 30]. However, to facilitate comparability, prevalence rates of GJH with a cutoff ≥4/9 were presented for all ages [30]. The diagnosis of benign joint hypermobility syndrome (BJHS) was determined according to the revised 1998 Brighton criteria. All clinical assessments were performed by a single experienced PMR specialist to ensure consistency.

The study was approved by the Ethics Committee (approval date: March 14, 2024; approval number: 3/12) and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Statistical Analyses

Statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics version 22 (IBM SPSS, Turkey). Normality of continuous variables was assessed using the Lilliefors-corrected Kolmogorov–Smirnov test. Age and body mass index (BMI) were normally distributed and were compared between groups using independent-samples Student's t-tests. The Beighton score was not normally distributed in either group (Lilliefors p=0.023 and p=0.002, lymphedema and control groups, respectively) and was therefore compared using the Mann–Whitney U test. Categorical variables (sex, GJH, and BJHS) were compared using Fisher's exact test, which was used in preference to the chi-square test throughout because several expected cell counts were below 5. Odds ratios (OR) with 95% confidence intervals (CIs) are reported alongside p-values for all binary outcomes so that the magnitude and precision of each estimate, not only its statistical significance, can be judged. To account for potential confounders, two additional analyses were performed. First, a baseline-comparability analysis compared the lymphedema and control groups on every recorded sociodemographic and clinical covariate (sex, education, marital status, occupation, smoking/alcohol use, and comorbidity) using Fisher's exact test (with Monte Carlo simulation for sparse r × c tables). Second, multivariable logistic regression models were fitted for GJH and BJHS, each adjusting for group, age, and BMI, to test whether the crude (unadjusted) group comparison was robust to these two continuous confounders.

A pre-specified sensitivity analysis collapsed Stage II and Stage III into a single "Stage II–III (moderate–advanced)" category and compared it against Stage I ("early") using the Mann–Whitney U test (Beighton score) and Fisher's exact test (GJH, BJHS), which yields adequately sized comparison groups (n=13 vs. n=23). Categorical comparisons across the three ordinal stages used the Fisher–Freeman–Halton exact test (the extension of Fisher's exact test to r × c tables), and the Kruskal–Wallis test was used for the Beighton score across the three stages.

Sample Size

The power analysis was performed using G*Power. The effect size of 0.40 (Δ:40%) used in the sample size calculation was derived from the literature [17]. A study of 184 patients with lumbar disc herniation found that BJHS, assessed with the revised (Brighton, 1998) criteria, was present in 68.4% of patients. That study did not include a control group; the prevalence of GJH in the general population ranges from approximately 10% to 30% [17]. Using the upper bound of this range (28.4%) as a conservative estimate of the expected prevalence in a non-hypermobile comparison population, and 68.4% as the expected prevalence in a population enriched for musculoskeletal referral [17], gives an expected between-group prevalence difference of Δ=68.4−28.4%=40.0%, consistent with the Δ=40%. With these two proportions (p1=0.684, p2=0.284), α=0.05 (two-tailed), and 80% power, a two-independent-proportions z test (unpooled variance in the power term) indicates a minimum required sample size of n=24 per group. The present study enrolled 36 patients with primary lymphedema and 32 controls.

RESULTS

Demographic and Clinical Characteristics of the Participants

The average age of the participants was 41.41±12.38 years. Overall, 76.5% of participants were female, and 23.5% were male. Comorbidities were present in 30.9%

Table 1. Demographic and clinical characteristics of the participants

Characteristics	n=68	Percentage
Sex		
Female	52	76.5
Male	16	23.5
Comorbidities		
Present	21	30.9
Absent	47	69.1
Distribution of comorbidities*		
Hypertension	7	33.3
Diabetes mellitus	7	33.3
Thyroid dysfunction	8	38.1
Hyperlipidemia	4	19
Others	5	23.8
Lymphedema		
Present	36	52.9
Absent	32	47.1
Lymphedema side		
Right	6	16.7
Left	11	30.6
Bilateral	19	52.8
Lymphedema stage**		
1	13	36.1
2	21	58.3
3	2	5.6
GJH		
Present	18 (F:17 M:1)	26.5 (F:94.4)***
Absent	50	73.5
BJHS		
Present	10 (F:10 M:0)	14.7 (F:100)***
Absent	58	85.3

BJHS: Benign joint hypermobility syndrome; GJH: Generalized joint hypermobility. *Some patients had more than one comorbidity; percentages do not sum to 100%; **Percentages for lymphedema side and stage are calculated among patients with lymphedema only (n=36), all other percentages are based on the total sample (n=68); ***Sex distribution percentages calculated on subgroup totals.

of participants. The most common comorbid conditions were thyroid disorders (38.1%), followed by hypertension (33.3%), diabetes mellitus (33.3%), hyperlipidemia (19.0%), and other conditions (23.8%; Table 1).

Primary lymphedema was present in 52.9% of participants (n=36). The duration of lymphedema

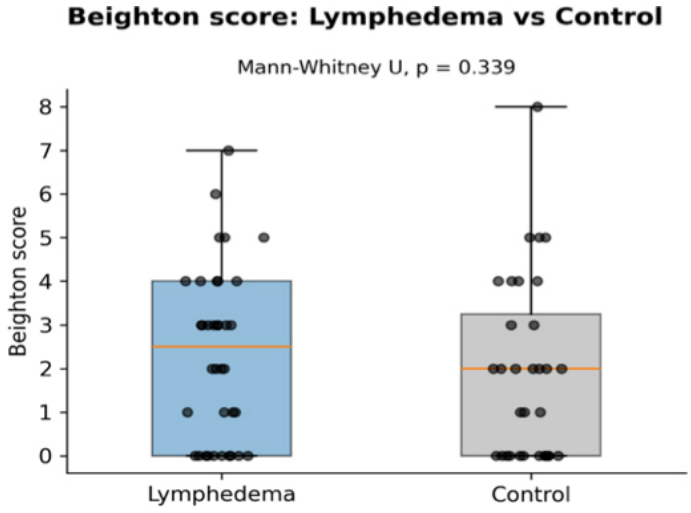

Figure 1. Beighton score by group. Boxplots show median and interquartile range; points represent individual participants (jittered).

ranged from 1 to 34 years, with a mean duration of 10.88±8.35 years. Among patients with lymphedema, 52.8% had bilateral involvement, whereas 47.2% had unilateral involvement (16.7% right-sided and 30.6% left-sided). According to disease stage, 36.1% of patients were classified as Stage I, 58.3% as Stage II, and 5.6% as Stage III (Table 1).

Across the entire study population, 18 participants (26.5%) met the criteria for GJH, and 10 participants (14.7%) were diagnosed with BJHS. GJH was identified in 17 females (94.4%) and one male (6.25%). BJHS was observed exclusively among female participants (100%), with no cases detected in males (Table 1).

Comparisons of Demographic and Hypermobility Outcomes Between Groups

The two groups did not differ significantly on any recorded sociodemographic or clinical covariate, indicating that observed differences in hypermobility outcomes are unlikely to be explained by imbalances in these variables (Table 2).

No statistically significant differences were observed in age, BMI, sex distribution, Beighton score, GJH prevalence, or BJHS prevalence. The ORs were close to 1.0 with wide (CIs) or both GJH (OR=1.15, 95% CI [0.39, 3.41]) and BJHS (OR=0.87, 95% CI [0.23, 3.34]), indicating that the data are compatible with a wide range of true effects and do not provide strong evidence against a modest association in either direction (Fig. 1, 2).

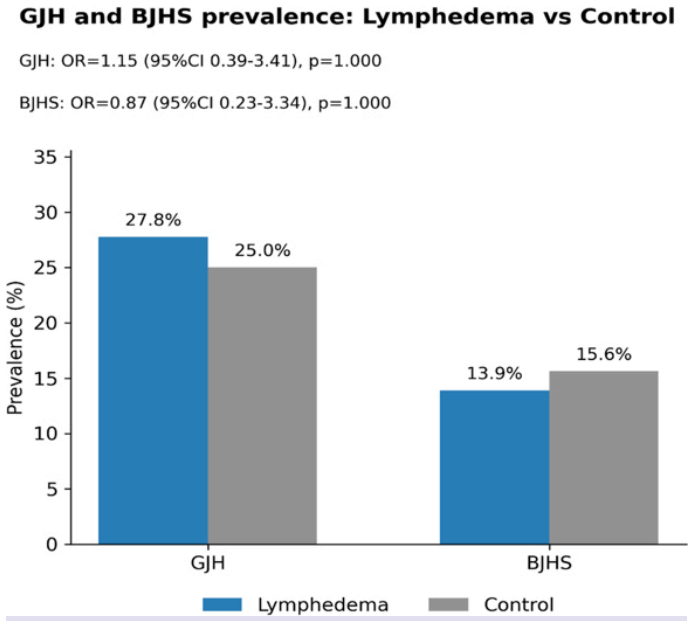

FIGURE 2. Prevalence of generalized joint hypermobility and benign joint hypermobility syndrome by group, with odds ratios (95% confidence interval) and Fisher's exact p-values.

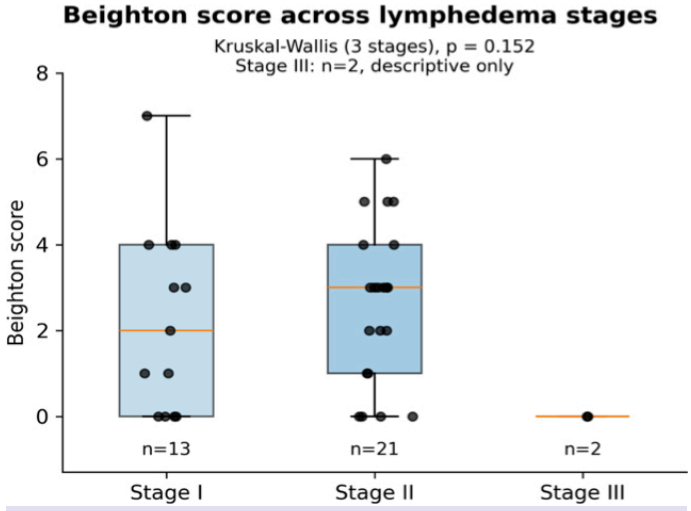

FIGURE 3. Beighton score across lymphedema stages. Stage III (n=2) is labeled for transparency and should be interpreted descriptively only.

Lymphedema Stage-Based Hypermobility Score Comparisons

Among the 36 patients with primary lymphedema, 13 (36.1%) were classified as Stage I, 21 (58.3%) as Stage II, and only 2 (5.6%) as Stage III. This severely limits the reliability of any three-level comparison involving Stage III. The exploratory three-level analysis (Table 3; Fig. 3, 4) found no statistically significant differences in Beighton score, GJH, or BJHS across stages; however, given that both Stage III patients had a Beighton score of 0 and neither met GJH nor BJHS criteria, these Stage III estimates should be regarded as descriptive only and not as evidence of a true stage effect.

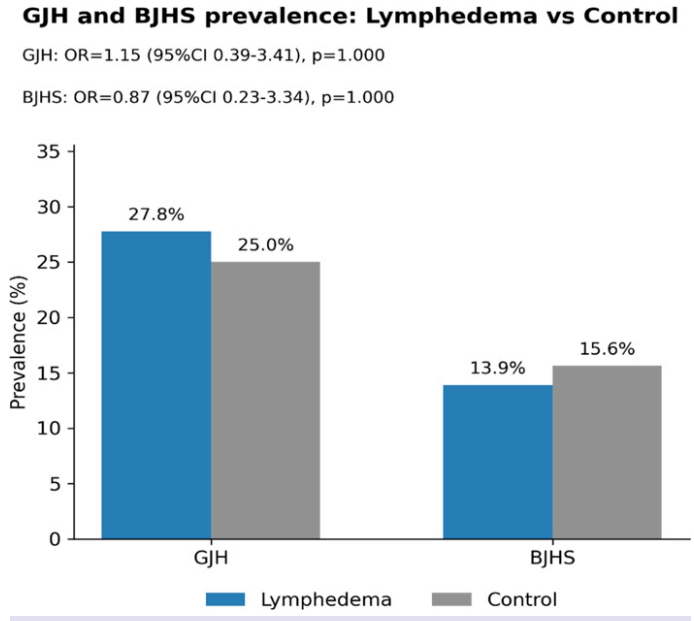

FIGURE 4. Prevalence of generalized joint hypermobility and benign joint hypermobility syndrome across lymphedema stages (Fisher–Freeman–Halton exact test).

To provide an adequately powered alternative to the three-level comparison, a pre-specified sensitivity analysis combined Stage II and Stage III into a single "Stage II–III (moderate–advanced)" category (n=23) and compared it with Stage I ("early," n=13; Table 4; Fig. 5, 6). This mirrors the original findings: No statistically significant differences were observed in Beighton score, GJH, or BJHS between early and moderate-to-advanced disease. The three-level comparison was retained as supplementary/exploratory.

Multivariable Logistic Regression Analysis for GJH and BJHS

To evaluate whether the crude group comparison was confounded by age or BMI, multivariable logistic regression models were fitted for GJH and BJHS (Table 5). After adjustment, the association between group (lymphedema vs. control) and GJH remained non-significant, and the point estimate was essentially unchanged (adjusted OR=1.03, 95% CI [0.30, 3.46]), as was the association with BJHS (adjusted OR=0.75, 95% CI [0.17, 3.13]). Age was independently and inversely associated

Table 2. Comparisons of demographic and hypermobility outcomes between groups

Variables	Lymphedema (n=36)	Control (n=32)	Test	OR (95% CI)	p
Age, years, Mean±SD	40.86±12.72	42.03±12.15	Student t	—	0.699
BMI, kg/m², Mean±SD	29.34±6.89	28.71±5.42	Student t	—	0.677
Sex, (%)			Fisher's exact	—	0.252
Female	83.3	68.8			
Male	16.7	31.2			
Education level, (%)			Fisher's exact	—	0.928
Primary	27.8	34.4			
Secondary	22.2	18.8			
Higher education	47.2	46.9			
Illiterate	2.8	0.0			
Marital status, (%)			Fisher's exact	—	0.614
Married	61.1	68.8			
Single	38.9	31.2			
Occupation, (%)			Fisher's exact	—	0.609
Housewife/unemployed	33.3	21.9			
Civil servant	11.1	6.2			
Worker	5.6	12.5			
Retired	2.8	3.1			
Student	2.8	0.0			
Engineer/architect/physician	11.1	9.4			
Education sector	8.3	3.1			
Service sector	25.0	43.8			
Smoking/alcohol use, (%)			Fisher's exact	—	0.612
Neither	75.0	78.1			
Smoker	19.4	21.9			
Alcohol	5.6	0.0			
Comorbidity, (%)			Fisher's exact	—	0.606
Present	27.8	34.4			
Absent	72.2	65.6			
Beighton score, Mean±SD	2.33±1.97	1.94±2.06	Mann–Whitney U	—	0.339
GJH positive, (%)	27.8	25.0	Fisher's exact	1.15 (0.39–3.41)	1.000
BJHS positive, (%)	13.9	15.6	Fisher's exact	0.87 (0.23–3.34)	1.000

BMI: Body mass index; GJH: Generalized joint hypermobility; BJHS: Benign joint hypermobility syndrome; OR: Odds ratio (Lymphedema vs. Control); CI: Confidence interval; Bold rows show the test statistic and p-value for the categorical variable as a whole; indented rows below each bold row show the frequency and percentage within each group for every category level. None of the baseline covariates (sex through comorbidity) differed significantly between groups (all p>0.05), supporting adequate comparability.

with GJH (adjusted OR=0.91, 95% CI [0.85, 0.97], p=0.006), and BMI was independently and positively associated with BJHS (adjusted OR=1.13, 95% CI [1.01, 1.29], p=0.043). These two incidental findings support the validity of the modeling approach (the model detects known/plausible associations) while confirming that the null group-level finding is not attributable to confounding by age or BMI.

TABLE 3. Beighton score, GJH, and BJHS across lymphedema stages (exploratory, three-level comparison)

Variabless	Stage I (n=13)	Stage II (n=21)	Stage III (n=2)[a]	Test	p
Beighton score	2.23±2.17	2.62±1.83	0.00±0.00	Kruskal–Wallis	0.152
GJH, (%)	30.8	28.6	0.0	Fisher–Freeman–Halton	1.000
BJHS, (%)	15.4	14.3	0.0	Fisher–Freeman–Halton	1.000

GJH: Generalized joint hypermobility; BJHS: Benign joint hypermobility syndrome. a: Stage III results are descriptive only (n=2) and should not be interpreted as a formal statistical comparison.

TABLE 4. Sensitivity analysis: Stage I versus Stage II–III (Combined)

Variables	Stage I (n=13)	Stage II–III combined (n=23)	Test	p
Beighton score	2.23±2.17	2.39±1.90	Mann–Whitney U	0.775
GJH, (%)	30.8	26.1	Fisher's exact	1.000
BJHS, (%)	15.4	13.0	Fisher's exact	1.000

GJH: Generalized joint hypermobility; BJHS: Benign joint hypermobility syndrome.

TABLE 5. Multivariable logistic regression for GJH and BJHS, adjusted for age and BMI

Outcome	Predictor	Adjusted OR (95% CI)	p
GJH	Group (Lymphedema vs. Control)	1.03 (0.30–3.46)	0.966
GJH	Age	0.91 (0.85–0.97)	**0.006**
GJH	BMI	0.99 (0.89–1.10)	0.853
BJHS	Group (Lymphedema vs. Control)	0.75 (0.17–3.13)	0.688
BJHS	Age	0.99 (0.92–1.05)	0.640
BJHS	BMI	1.13 (1.01–1.29)	**0.043**

GJH: Generalized joint hypermobility; BJHS: Benign joint hypermobility syndrome; BMI: Body mass index; OR: Odds ratio; CI: Confidence interval.

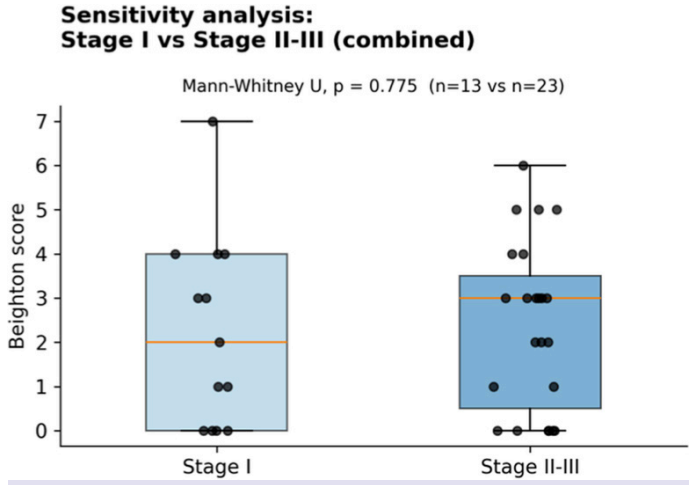

FIGURE 5. Sensitivity analysis: Beighton score, Stage I versus Stage II–III (combined).

DISCUSSION

In view of the limited evidence available in the current literature, this study aimed to investigate the association between primary lymphedema and JH as well as lymphedema stage. In this study, hypermobility was identified in 27.8% of patients with primary lymphedema. No significant association was found between GJH or BJHS and primary lymphedema or lymphedema severity. BMI was positively associated with BJHS. In addition, consistent with previous literature, this study demonstrated a female predominance of JH and an inverse association between age and JH [2, 3].

In recent years, interest in JH and its related disorders has grown, encompassing a range of uncommon clinical presentations. As noted in the introduction, several hereditary connective tissue disorders share JH

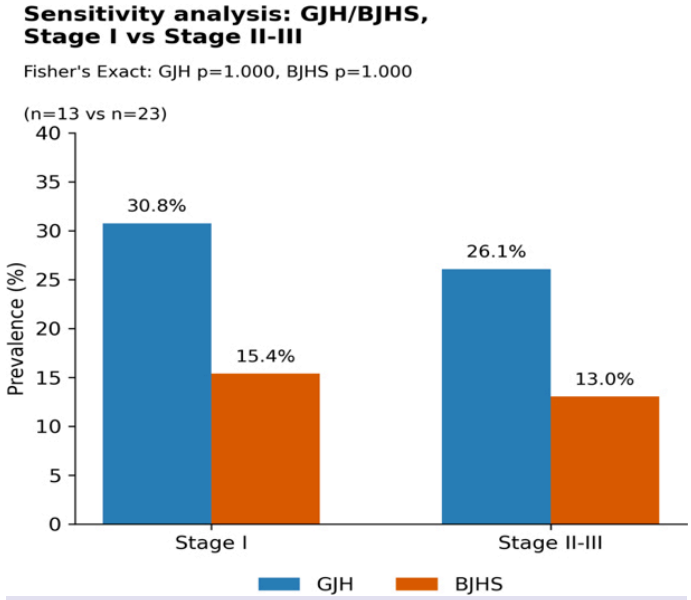

FIGURE 6. Sensitivity analysis: prevalence of GJH and BJHS, Stage I vs. Stage II–III (combined).

as a feature while lacking other characteristic clinical manifestations [3, 4, 15–19]. The literature demonstrates a significant association between GJH – commonly assessed using the Beighton score – and both articular and extra-articular conditions [4]. However, the pathophysiological mechanisms linking hypermobility spectrum disorders (HSDs) to extra-articular manifestations remain even less well understood [10].

Previous studies have investigated the association between lymphovascular disorders and JH [18, 31–33]. Some studies reported variable associations between JH and venous diseases [2, 18], such as venous insufficiency, suggesting it as a potential risk factor. This may be explained by the weakness of supporting connective tissue structures observed in JH patients [2, 34], as connective tissue weakness within venous walls has also been implicated in the pathophysiology of varicose veins [34].

Connective tissue forms a fundamental component of both blood and lymphatic vessel walls, directly affecting vascular compliance and contributing to elevated permeability, particularly under conditions of increased pressure [35]. Lymphedema is a chronic, progressive disorder defined by the buildup of protein-rich interstitial fluid resulting from impaired lymphatic function [26]. This study investigated the potential association between lymphedema and JH, as the lymphatic system consists of mesoderm-derived connective tissue.

Assessment of JH in patients with primary lymphedema may provide valuable insights into diagnostic approaches and treatment strategies. At this point, enhancing physician awareness of JH and associated articular and extra-articular manifestations in primary lymphedema is essential. Given the complexity and severity of these clinical features, careful consideration may be necessary to improve appropriate management strategies. However, contrary to our hypothesis, no significant association was found between JH and primary lymphedema. In this study, the Beighton score was used to screen for hypermobility, as it is best utilized as a screening tool, and a positive score indicates that an individual has GJH. However, low scores on the Beighton do not rule out generalized, mono, pauci, or regional hypermobility [9, 36]. The study offers a reference point to guide future research on affected clinical populations of interest. Therefore, future studies should incorporate objective diagnostic criteria and validated instruments to better characterize JH in patients with primary lymphedema.

Castori et al. [4] stated that the term "syndrome with JH" should be used for genetic conditions characterized by JH. Primary lymphedema represents a diverse spectrum of congenital lymphatic dysplasias leading to progressive lymphatic fluid accumulation and tissue swelling. It may occur either as an isolated condition or as part of a syndromic disorder [29]. For many of the Ehlers–Danlos syndrome subtypes, pathogenic variants of genes have been identified [4]. Syndromic forms of lymphedema accompanied by JH have been described – such as Nevo syndrome and mandibulofacial dysostosis–lymphedema syndrome [27] – these conditions are rare. In a reported case, the coexistence of JH and lymphedema in a patient's sibling suggested a possible shared pathophysiological basis between connective tissue disorders and lymphatic dysfunction [20]. However, the genes implicated in these syndromes do not overlap with the core genes associated with primary lymphatic disorders and lymphovascular malformations [28, 37]. Future studies should explore the pleiotropic effects of genes involved in syndromic forms of primary lymphedema to better elucidate the shared mechanisms underlying lymphatic and connective tissue abnormalities.

In lymphedema, tissue alterations are predominantly driven by chronic inflammation, leading to progressive fibrosis and increased tissue stiffness. No statistically significant differences were observed between lymphedema stages in terms of mean Beighton scores or the prevalence of GJH and BJHS. In this regard, the sensitivity

of clinical hypermobility assessments may be limited in patient populations in which fibrosis predominates, particularly when diagnostic criteria such as the Beighton score, reflecting the number of hypermobile joints rather than the severity of connective tissue laxity, are used [38]. Future studies incorporating quantitative assessments of connective tissue properties – such as elastography or histopathological analysis – may provide further insight.

Study Limitations

Considering the complex range of signs and varying degrees of symptoms of HSDs, as well as the cross-sectional design, causality between JH and primary lymphedema cannot be established. Using a single PMR specialist for all assessments improved standardization, but the lack of assessor blinding may have introduced observer bias, particularly in partially subjective measures such as the Beighton score. Furthermore, potential confounding factors such as BMI, physical activity level, menopausal status, occupational workload, and sports history were not assessed, which may have affected the prevalence of JH. The Stage III subgroup was very small (n=2), limiting meaningful statistical comparisons. In addition, because JH decreases with advancing age [2, 3], the relatively high median age of 41 years in the study population may have led to an underestimation of generalized JH prevalence. Because no prior study has examined JH prevalence in primary lymphedema, the effect size for sample size calculation was derived from a study of BJHS in lumbar disc herniation [17], which may not fully reflect the expected effect in this population.

Conclusion

JH was identified in 27.8% of patients with primary lymphedema; however, no significant association was observed between JH and primary lymphedema or disease severity. Age was inversely associated with JH. A female predominance was observed. These findings may serve as a basis for future studies incorporating objective diagnostic criteria, validated instruments, and quantitative assessments of connective tissue properties to better characterize JH. In addition, exploring the pleiotropic effects of genes involved in syndromic forms of primary lymphedema may further elucidate the underlying mechanisms.

Ethics Committee Approval: This study was approved by The University of Health Sciences Hamidiye Scientific Research Ethics Committee (Approval number: 3/12 – 14.03.2024).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

Conflict of Interest: The authors declare that there is no conflict of interest.

Financial Disclosure: The authors declared that this study received no financial support.

Use of AI for Writing Assistance: The authors declared that artificial intelligence was not used in the study.

Authorship Contributions: Concept – FAB, IA; Design – FAB; Supervision – FUO, GO; Resource – IA, FUO; Materials – MYK, ADSK; Data Collection and/or Processing – FAB; Analysis and/or Interpretation – FAB, GO; Literature Search – FAB, MYK; Writing – FAB, GO, MYK, ADSK, FUO, IA; Critical Reviews – FAB, GO, MYK, ADSK, FUO, IA.

Peer-review: Externally peer-reviewed.

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Appendix 1. Beighton score for joint hypermobility

Beighton test	Definition	Score range
Fifth finger	Passive dorsiflexion >90°	0–2
Thumb	Passive apposition to the forearm	0–2
Elbow	Hyperextension >10°	0–2
Knee	Hyperextension >10°	0–2
Trunk flexion	Palms on the floor with knees extended	0–1
Total score		0–9

A Beighton score ≥4 indicates generalized joint hypermobility.

Appendix 2. Revised Brighton (1998) criteria for benign joint hypermobility syndrome

Category	Criterion
Major	Beighton score ≥4/9 (current or historical)
	Arthralgia >3 months in ≥4 joints
Minor	Beighton score 1–3/9 (0–3 if age ≥50 years)
	Arthralgia in 1–3 joints, back pain, or spondylosis/spondylolysis/spondylolisthesis
	Recurrent dislocation or subluxation in ≥1 joint
	≥3 soft-tissue lesions (epicondylitis, tenosynovitis, and bursitis)
	Marfanoid habitus
	Skin abnormalities (striae, hyperextensibility, thin skin, and papyraceous scars)
	Eye signs (ptosis, myopia, and antimongoloid slant)
	Varicose veins, hernia, or uterine/rectal prolapse

Benign joint hypermobility syndrome is diagnosed if two major, or one major plus two minor, or four minor, or two minor plus an affected first-degree relative are present.