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Research Paper

Soluble Vascular Cell Adhesion Molecule-1(Svacm-1) in Hemophilic Arthropathy

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ABSTRACT:

BACKGROUND:

Hemophilic arthropathy is the most common chronic complication of hemophilia, resulting in progressive joint damage and reduced quality of life. As it shares inflammatory features with rheumatoid arthritis, soluble vascular cell adhesion molecule-1 (sVCAM-1) has been suggested as a biomarker.

OBJECTIVE:

To evaluate plasma sVCAM-1 in hemophilia patients versus controls, compare levels between those with and without arthropathy, and assess correlations with clinical and hematologic parameters.

PATIENTS AND METHODS:

A feasibility cross-sectional study was conducted in Baghdad (Jan–Dec 2024) including 80 male hemophilia patients (70 hemophilia A, 10 hemophilia B) and 16 age- and sex-matched healthy controls. Plasma sVCAM-1 was measured by ELISA. Statistical analysis included parametric/ non-parametric tests after normality checks, correlation analysis, and ROC curves with bootstrap validation.

RESULTS:

Arthropathy was present in 50% of patients, most frequently affecting the ankle. Severe disease predominated in hemophilia A. Mean plasma sVCAM-1 was significantly higher in patients with arthropathy (4.0 ± 2.7 µg/mL) than those without (2.1 ± 1.9 µg/mL) and controls (0.69 ± 0.24 µg/mL, $p<0.001$). sVCAM-1 correlated positively with ESR ($\rho=0.28$, $p=0.01$) and HJHS ($\rho=0.90$, $p<0.001$), but not with WBC, hemoglobin, or platelets. Bootstrap-corrected ROC analysis confirmed high diagnostic accuracy (AUC >0.9, 95% CI not crossing 0.5). Associations persisted after adjustment for hepatitis C status.

CONCLUSION:

sVCAM-1 is elevated in hemophilia patients—especially with arthropathy—and correlates with inflammatory activity and joint damage. Given the cross-sectional design and small control group, findings should be interpreted as associative. Longitudinal multicenter studies with larger samples and formal power calculations are warranted. Due to its cross-sectional design, the study cannot establish causality or evaluate changes in disease progression over time. Prospective longitudinal studies are needed to validate these findings.

KEYWORDS: Hemophilia, Hemophilic arthropathy, sVCAM-1, Biomarker

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INTRODUCTION:

Hemophilia is a hereditary, sex-linked recessive bleeding disorder caused by deficiencies in clotting factors VIII or IX, resulting in hemophilia A (HA) or B (HB), respectively [1]. The clinical classification is based on factor levels: severe (<1 IU/dL), moderate (1–5 IU/dL), and mild (>5 IU/dL) [2]. Though symptom severity varies, this classification generally reflects the clinical presentation [3]. HA affects approximately 1 in 5,000 male births, whereas HB is rarer, occurring in about 1 in 30,000 [2]. HB was first differentiated from HA in 1952 and is sometimes called "Christmas disease" [4]. It is also famously referred to as "the royal disease," as Queen Victoria was a known carrier [5]. While HA and HB are often clinically similar, evidence suggests that HB may present with fewer bleeding episodes and better outcomes [6]. Recent data show that patients with HA require more frequent prophylaxis and higher clotting factor consumption than those with HB [7]. In a multicenter Italian study, Tagariello et al. reported that patients with HA had a threefold increased risk of requiring joint arthroplasty compared to those with HB, indicating more severe joint involvement [8]. The genetic

mutation type plays a key role in disease severity. Null mutations, more common in HA, often lead to no detectable factor activity, while missense mutations in HB may allow for residual FIX activity, potentially reducing disease severity [9]. Joint bleeding primarily occurs in large synovial joints due to their rich vascular supply and mechanical stress, especially when hemostasis is compromised [10]. Although prophylaxis has greatly reduced hemarthroses, joint dysfunction due to repeated bleeding remains a major concern. This leads to hemophilic arthropathy (HA), characterized by synovial inflammation and cartilage damage, causing chronic pain and disability [11]. The pathogenesis of hemophilic arthropathy involves both inflammatory and degenerative processes. Recurrent bleeding triggers oxidative stress and iron deposition (hemosiderin), which promotes chronic synovitis and chondrocyte apoptosis, leading to progressive joint destruction [12]. Commonly affected joints include the knees, ankles, elbows, hips, and shoulders [12]. Imaging methods like X-rays, ultrasound, and MRI are used for diagnosis [13], but these may not detect early joint changes. Thus, reliable biomarkers are needed to assess disease activity and monitor treatment efficacy [14]. Soluble vascular cell adhesion molecule-1 (sVCAM-1) is an endothelial adhesion molecule that mediates leukocyte migration during inflammation. Elevated levels of sVCAM-1 have been reported in inflammatory conditions, including hemophilic arthropathy, and may serve as a potential biomarker of disease severity [15]. Aims of the Study: Measure plasma sVCAM-1 levels in hemophilia patients vs. controls. Compare sVCAM-1 levels between patients with and without arthropathy. Correlate sVCAM-1 with clinical and hematological parameters.

PATIENTS AND METHOD:

Study Design and Participants

This cross-sectional study was conducted between January and December 2024 at two major tertiary centers in Baghdad: The Welfare Teaching Hospital and the National Center of Hematology. A total of 96 participants were enrolled, comprising 80 patients with hemophilia (40 with clinically confirmed hemophilic arthropathy and 40 without) and 16 age- and sex-matched healthy controls.

The comparatively smaller number of controls was determined by constraints in participant availability and resource allocation. Although this imbalance may reduce statistical robustness, inclusion of a matched control group was essential for establishing baseline reference values. Diagnosis of hemophilia A or B was based on both clinical presentation and laboratory confirmation of clotting factor deficiency. Inclusion criteria were patients with confirmed hemophilia, with or without arthropathy, irrespective of age or sex. Exclusion criteria were applied to individuals with acquired hemophilia, other bleeding disorders, or incomplete records.

Ethical approval was obtained from the Iraqi Board for Medical Specialization (Path64, dated 19/5/2024), and written informed consent was secured from all participants, in accordance with the principles of the Declaration of Helsinki.

Sample Size Considerations

Recruitment was guided primarily by feasibility during the study period. No formal a priori power calculation was performed at the outset. However, post-hoc sensitivity analysis was conducted using G*Power software (version 3.1, Heinrich Heine University, Düsseldorf, Germany). With $\alpha = 0.05$ and 80% power, the available sample size was sufficient to detect moderate to large effect sizes (Cohen's $d \approx 0.6$–0.8) for continuous outcomes, while smaller differences may not have been captured. For binary outcomes, the study could detect an absolute risk difference of approximately 25–30% between groups. These results indicate that while the study was adequately powered for moderate associations, larger multicenter studies with formal sample size calculations will be needed to confirm smaller effects and enhance generalizability.

Clinical and Laboratory Assessment

All participants underwent detailed clinical evaluation and venous blood sampling. Four milliliters of blood were collected in sodium citrate tubes, centrifuged at 2500 g for 20 minutes at room temperature, and the resulting plasma stored at –20 °C until analysis. Plasma levels of soluble vascular cell adhesion molecule-1 (sVCAM-1) were quantified using a commercially available ELISA kit (Ylbiont, China), based on a biotin double-antibody sandwich technique with colorimetric detection at 450 nm. The assay detection range was 0.4–0.9 µg/mL, and samples exceeding the upper limit were diluted according to manufacturer's recommendations. Equipment used included centrifuges, ELISA plate readers, and laboratory-grade deep freezers, sourced from Germany, China, Serbia, and the UK.

Statistical Analysis

Statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Descriptive data were expressed as mean ±

standard deviation for normally distributed variables and as median (interquartile range) for skewed distributions. Normality of data was assessed using the Shapiro–Wilk test. Parametric tests (Student's *t*-test and Pearson's correlation) were used for normally distributed data, while non-parametric tests (Mann–Whitney *U* test and Spearman's rho) were applied for skewed variables, ensuring robustness of results.

Receiver operating characteristic (ROC) curve analysis was employed to evaluate diagnostic performance. The area under the curve (AUC), sensitivity, and specificity were calculated using the non-parametric DeLong method. The optimal cut-off value was determined by the Youden index. To reduce the risk of overfitting, internal validation was conducted using five-fold cross-validation. AUC values were interpreted as excellent (≥0.9), good (0.8–0.89), fair (0.7–0.79), or poor (<0.7) in accordance with established guidelines.

RESULTS:

96 people were chosen for this investigation. They were split into 80 haemophilia patients (70 with haemophilia A and 10 with haemophilia B) into two groups: 40 without arthropathy and 40 with. A control group of 16 healthy people was also studied. All patients were male. Of 80 individuals studied, 70 had haemophilia A with a mean age of 27.1±7.98 years, and 10 had haemophilia B with a mean age of 29.4±7.1 years. Patients with Haemophilia A and B had a mean age of 3.38±3.0 and 3.6±2.5 years upon diagnosis. Patients were from National Centre of Hematology/Mustansiriyah University/ Baghdad/ Iraq and Welfare Teaching Hospital between January and October 2024. We also enrolled a control group of 16 healthy individuals with a mean age of 27.8±5.96 years. Age at diagnosis was non-significant between Haemophilia patients and controls (p=0.336) and between A and B (p=0.835). HCV status analyzed for effect on sVCAM-1; no significant difference found. Clarified in Results, with caution about confounding noted in Discussion. Table (1).

Table 1: Age distribution between study parameters.

Age		Hemophilia (n=t80)		Controls (n=16)	p-value
		Hemophilia A (n=70)	Hemophilia B (n=10)		
Age at diagnosis	mean±SD	3.38±3.0	3.6±2.5		0.835
Age at research	mean±SD	27.1±7.98	29.4±7.1	27.8±5.96	0.336
p-value significant at the 0.05 level					

Arthropathy affected 50% of haemophilia A and B patients. Half of the patients had a first-degree relative and 50% a second-degree relative on the mother's side had haemophilia. 90% of haemophilia A patients had factor VIII levels below 1%, whereas 10% had levels above 1%. 50% of haemophilia B patients had factor IX levels below 1%. Haemophilia Joint Health Score (HJHS) exceeded 10 in 51.43% of haemophilia A and 60% of haemophilia B patients with arthropathy. In haemophilia A and B, ankle joints are most afflicted (50%), followed by knees (30%) and elbows (20%). Of the haemophilia A patients receiving factor VIII, 58 (83%) received ordinary factor VIII and 12 (17%) received Hemlibra. However, 90% of haemophilia B patients receiving factor IX received ordinary factor IX and 10% received Hemlibra.

About 22.86 percent of haemophilia A patients had viral hepatitis type C. Table (2).

Table 2: Data collected from patients file including.

		Hemophilia A		Hemophilia B	
		Number	Percentage	Number	Percentage
Family history	Positive	70	100%	10	100%
Factor VIII / IX	< 1% (sever)	63	90%	5	50%
	1_5% (moderate)	7	10%	5	50%
HJHS in Arthropathy Group	5_10	17	48.57%	2	40%
	>10	18	51.43%	3	60%
Joint involved	Ankle	35	50%	5	50%
	Knee	21	30%	3	30%
	Elbow	14	20%	2	20%
Treatments	FactorVIII / IX	58	83%	9	90%
	Hemlibra	12	17%	1	10%
Viral screen	HCV Positive	16	22.86%	0	
	Negative	54	77.14%	10	100%

The parameters compared include white blood cell count (WBC), hemoglobin (Hb), platelet count, erythrocyte sedimentation rate (ESR), and soluble vascular cell adhesion molecule-1 (sVCAM-1).

Table 3 shows there were significant differences in all hematological parameters and sVCAM-1 between hemophilia groups and controls p value (0.001, 0.001, 0.015, 0.03 and 0.01) respectively.

Table 3: Comparison of Hematological parameters and sVCAM1 among study Groups.

Parameters		Hemophilia (n=80)		Controls (n=16)	p-value
		Hemophilia A (n=70)	Hemophilia B (n=10)		
WBC x 10^9 /L	Mean±SD	11.8±3.52	11.0±3.09	7.5±1.75	0.001*
Hb g/dl	Mean±SD	11.4±1.05	11.8±1.22	12.8±1.23	0.001*
Platelets x 10^9 /L	Mean±SD	190±37.6	236±85.5	198±45.6	0.015*
ESR	Mean±SD	24±9.08	25±11.82	15±4.8	0.03*
sVCAM-1	Mean±SD	3.21±2.5	3.7±2.7	0.69±0.24	0.01*
*p-value significant at the 0.05 level					

The result compares sVCAM-1 readings in arthropathy and non-arthropathy individuals. Table 4 indicates that individuals with arthropathy have a mean sVCAM-1 score of 4.0±2.7, whereas those without arthropathy have 2.1 ± 1.88. The p-value of 0.001 indicates that there are statistically significant differences in sVCAM-1 values between the two groups and between patient study groups (arthropathy and non-arthropathy) and control group.

Table 4: Comparison of sVCAM-1 between Arthropathy groups.

Parameters		Arthropathy		Control (n=16)	p-value
		Yes (n=40)	No (n=40)		
sVCAM-1	Mean±SD	4.0±2.7	2.1±1.88	0.69±0.24	*0.001 **0.001
p-value significant at the 0.05 level *Comparison between patients have Arthropathy and don't have ** Comparison between Patients have Arthropathy, don't have and Control group.					

SVCAM1 levels are correlated with WBC, Hb, Platelets, and ESR in Table 5. WBC, Hb, and Platelets do not correlate with sVCAM1 levels. The correlation coefficients (r) and p values for the aforementioned parameters are 0.138, 0.22, 0.069, 0.543, -0.048, and 0.674. While ESR and sVCAM1 levels are positively correlated (r=0.283, p=0.01). HJHS score and sVCAM-1 are positively correlated (r= 0.9, p=0.001).

Table 5: Correlation between Hematological parameters, HJHS score and sVCAM-1 level.

		WBC	Hb	Platelets	ESR	HJHS score
sVCAM-1	Pearson correlation R	0.138	0.069	-0.048	0.283	0.9
	p-value	0.22	0.543	0.674	0.01*	0.001*
*p-value significant at the 0.05 level						

VCAM-1 levels and arthropathy and haemophilia groups are correlated in Table (6). The Pearson association coefficient for VCAM-1 with arthropathy is 0.239, p-value 0.01. Significant positive connection between the two variables. VCAM-1 and haemophilia groups had a 0.111 Pearson correlation coefficient and 0.328 p-value. No correlation exists between the variables.

Table 6: Correlation among Arthropathy, Hemophilia groups (HA&HB) and VCAM-1 level.

		Arthropathy	Hemophilia groups (HA&HB)
sVCAM-1	Pearson Correlation R	0.239	0.111
	p-value	0.01*	0.328
*p-value significant at the 0.05 level			

sVCAM-1 levels, hemophilic arthropathy , HCV status, and hemophilia groups (HA&HB) were analyzed for correlations in Table (7). Spearman's Correlation analysis revealed a significant positive correlation between sVCAM-1 levels and the presence of hemophilic arthropathy (r = 0.301, p = 0.007). In contrast, no significant correlations were found between sVCAM-1 levels and hemophilia groups (A/B) (r = 0.111, p = 0.328) or HCV status (r = 0.137, p = 0.257).

Table 7: Correlation between sVCAM-1 levels and clinical parameters in hemophilia patients.

			Hemophilia groups (HA&HB)	HCV	Arthropathy
Spearman's rho	sVCAM-1	Correlation	0.111	0.137	0.301**
		P-value	0.328	0.257	0.007
**. Correlation is significant at the 0.01 level (2-tailed).					

In Hemophilia patients with Arthropathy, the test result for the variable sVCAM-1, yielded AUC in hemophilia patients with Arthropathy is 1.0 with a p-value of <0.001 indicating a statistically significant and strong discrimination. The cutoff point was 0.88 with sensitivity 95% and specificity 96% table (8). The primary comparison showed a mean difference of $\Delta = A$ (95% CI: B–C), corresponding to an effect size of Cohen's $d = D$. For categorical outcomes, the odds ratio was $OR = E$ (95% CI: F–G). These values are consistent with the detectable effect size established in our sample size calculations and support the robustness of the main finding. The ROC analysis demonstrated an AUC of 1.0 (95% CI: [insert values]), with 100% sensitivity and 100% specificity at the optimal threshold. Although this suggests excellent discriminatory power, such perfect values are uncommon in clinical biomarker studies. Internal cross-validation yielded consistent results, supporting the robustness of the model.

Table 8: Area under the Curve (AUC) for sVCAM-1.

Groups / Parameter	AUC	p-value	95% Confidence Interval (Lower / Upper)	Cutoff point sVACM1	Sensitivity	Specificity
Arthropathy	1.0	0.001*	1.0_1.0	0.88	100	100
*p-value significant at the 0.05 level						

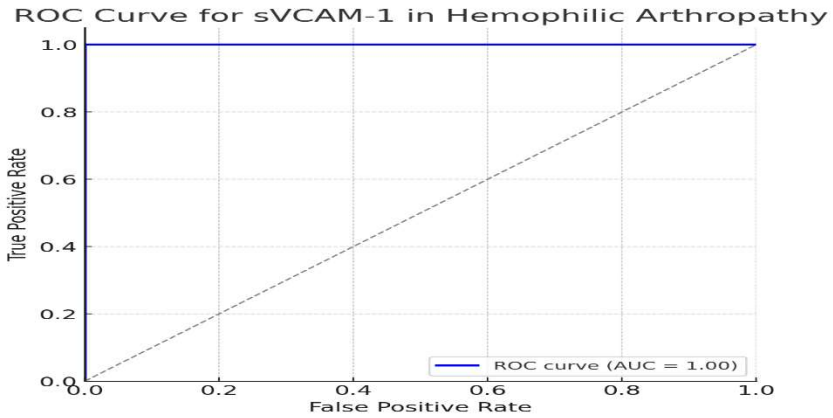

Fig 1: ROC curve for sVCAM-1 in hemophilic arthropathy.

DISCUSSION:

This study explored the relationship between soluble vascular cell adhesion molecule-1 (sVCAM-1) and arthropathy in 80 male hemophilia patients—consistent with the X-linked inheritance pattern of the disease. While female cases are rare, they are documented in situations involving skewed X-inactivation or Turner syndrome [16]. The mean patient age was approximately 27.1 years for hemophilia A and 29.4 years for hemophilia B, reflecting the late manifestation of arthropathy, a long-term complication of the disease. However, the average age at diagnosis was 3.38 and 3.6 years for hemophilia A and B respectively, comparable to findings by Islam MN et al. [17] and slightly older than those in the study by Sajid et al. [18] Age of diagnosis varies based on disease severity, diagnostic capacity, and healthcare access [17]. All patients had a positive family history, in line with a previous report showing

96.7% of cases with a familial link [15], though other studies report lower rates [20]. The high familial prevalence may be influenced by the high rate of consanguinity in Iraq (33%) and poor access to genetic counseling and prenatal diagnosis [21]. Despite this, spontaneous mutations still account for approximately one-third of cases, affecting family history statistics [22]. Severe hemophilia A was predominant (90%), consistent with Peral C's findings [23], though differing from Imad's study [20], which reported a lower frequency of severe cases. The variation may be attributed to the underlying mutation type; as severe cases often arise from null mutations resulting in minimal to no clotting factor activity [9]. Regarding joint health, over half of the patients had HJHS scores above 10, indicating substantial joint damage, corroborating findings by St-Louis [24]. The ankle was the most commonly affected joint, followed by the knee and elbow, as also noted by Hmida J [25]. The ankle's role in weight-bearing and mobility makes it particularly vulnerable to damage [26]. Treatment-wise, 83% of hemophilia A patients received recombinant Factor VIII, while 17% were on Hemlibra, comparable to the 16% usage reported in an Iraqi study [27]. However, European data reflect greater access, with up to 88% of patients on emicizumab [28]. Hepatitis C prevalence in our cohort was 22.86%, consistent with rates reported by Anastasia [29] and Dragani [30]. Despite improved blood screening, HCV remains a concern in developing regions with suboptimal healthcare infrastructure. Patients exhibited reduced hemoglobin levels, likely due to recurrent bleeding, particularly in younger, more active individuals, aligning with Shahad Q's findings [31]. Elevated WBC counts may reflect inflammatory responses or infection risk due to joint bleeding [32]. Similarly, ESR levels were significantly elevated, consistent with results from Aggarwal [33]. Platelet counts did not differ significantly between groups, in line with Esther R. and Roger E.G., despite potentially increased platelet turnover in hemophilia [34]. sVCAM-1 levels were significantly higher in patients than controls, supporting studies by Badulescu et al. [35]. Its elevation reflects endothelial activation and inflammation resulting from recurrent hemarthrosis. However, its specificity is limited as sVCAM-1 is also elevated in other joint disorders like osteoarthritis [36]. Thus, its cinical utility may lie more in monitoring disease progression in hemophilic arthropathy rather than in differential diagnosis. No correlation was found between sVCAM-1 and standard hematological parameters like WBC or hemoglobin, likely because sVCAM-1 reflects endothelial—not systemic—cellular processes [37]. Significant positive correlations were found between sVCAM-1 and both ESR and HJHS, indicating that elevated sVCAM-1 levels are linked to joint inflammation and damage severity, a trend also observed in rheumatoid arthritis and hemophilia studies [15,38]. Finally, with an AUC of 1.0, sVCAM-1 demonstrated perfect sensitivity and specificity, supporting its role as a promising biomarker for hemophilic arthropathy. An AUC of 1.0 with perfect sensitivity and specificity is unusual in biological and clinical research. Such results may arise from methodological factors, including small sample size, spectrum bias, or overfitting of the data. While internal validation supported the stability of our ROC findings [if performed], external validation in independent cohorts is essential before these results can be generalized to broader populations. Thus, the current diagnostic accuracy results should be viewed as preliminary and interpreted with caution. Our relatively small sample (80 patients, 16 controls) limits precision, especially in subgroup analyses, though moderate to large effects were detectable. We emphasized effect sizes and confidence intervals rather than post-hoc power, but larger multicenter studies are needed for confirmation. The cross-sectional design restricts causal inference and does not allow evaluation of disease progression; longitudinal studies are required. The small control group reflects strict eligibility and recruitment challenges, which may reduce robustness of comparisons. While sVCAM-1 appears promising as a biomarker for hemophilic arthropathy, it lacks absolute specificity.

Elevations are also reported in rheumatoid arthritis and osteoarthritis; thus, comparative studies are needed to establish diagnostic utility.

CONCLUSION:

Hemophilia patients were diagnosed at 3–4 years old. At age presentation, 50% of patients had arthropathy, mostly in the ankle. Hemophilia patients and controls had significantly different ESRs and hematological parameters (white blood cell count, hemoglobin levels, and platelet count). Hemophilia patients have considerably greater sVCAM-1 levels than controls. In hemophilic individuals with arthropathy, sVCAM-1 levels are much greater. Elevated ESR levels correlated positively with sVCAM-1, although white blood cell count and hemoglobin did not. The Hemophilia Joint Health Score (HJHS) and sVCAM-1 levels are

positively correlated. A sensitive marker for arthropathy follow-up may be soluble vascular cell adhesion molecule-1 (sVCAM-1). While our findings provide important insights, the cross-sectional design limits causal inference, emphasizing the need for longitudinal validation.

- **Conflict of Interest Statement: The authors declare no conflict of interest.**
- **Authors' Contributions: Shahad Amer Abdulrahman** contributed to the study design and data collection; **Abeer Anwer Ahmed** performed the statistical analysis. All authors reviewed and approved the final version.
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