BRIEF REPORT

DOI: 10.4274/tjh.galenos.2025.2025.0201
Turk J Hematol 2025;42:315-319

Real-World Clinical Outcomes and Prognostic Factors in Acquired Hemophilia A: A Single-Center Retrospective Analysis

Edinsel Hemofili A'da Gerçek Yaşam Klinik Sonuçları ve Prognostik Faktörler: Tek Merkezli Retrospektif Bir Analiz

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Abstract

Acquired hemophilia A (AHA) is a rare but potentially life-threatening bleeding disorder. This single-center retrospective study aimed to assess clinical features, treatment strategies, and prognostic indicators in adult AHA patients. Eleven patients diagnosed between 2008 and 2024 were reviewed. Clinical data, laboratory findings, treatments, and outcomes were analyzed. Survival estimates and prognostic factors were evaluated using Kaplan-Meier and univariate analyses. Median age was 41 years; 54.5% of the patients were female. Pregnancy-associated AHA (36.4%) had excellent outcomes with steroid monotherapy and no relapse. Idiopathic and autoimmune cases required combination therapy and had higher relapse rates. The median follow-up duration was 27 months. All patients achieved remission (median response time: 62 days), though 36.4% relapsed. High inhibitor titer (>20 Bethesda unit) predicted delayed response (p=0.038); male sex and major bleeding were linked to shorter relapse-free survival. Baseline inhibitor burden and disease etiology influence AHA prognosis. Tailored therapy and multicenter validation are warranted to refine management strategies.

Keywords: Acquired hemophilia A, Bleeding disorder, Inhibitor, Bypassing agents, Immunosuppressive therapy

Öz

Edinsel hemofili A (EHA) nadir görülen ancak yaşamı tehdit edebilen bir kanama bozukluğudur. Bu tek merkezli retrospektif çalışmamızın amacı, erişkin EHA hastalarında klinik özellikleri, tedavi stratejilerini ve prognostik göstergeleri değerlendirmektir. 2008-2024 yılları arasında tanı konulan 11 hasta incelendi. Klinik ve laboratuvar verileri, tedaviler ve klinik sonuçlar analiz edildi. Beklenen sağkalımlar ve prognostik faktörler Kaplan-Meier yöntemi ve tek değişkenli analiz ile değerlendirildi. Ortanca yaş 41 idi; %54,5'i kadındı. Gebelikle ilişkili EHA (%36,4) steroid monoterapisine çok iyi yanıt verdi ve nüks gözlenmedi. İdiyopatik ve otoimmün hastalık ilişkili olgularda kombine immünosüpresif tedavi gerekti ve nüks oranı daha yüksekti. Ortanca takip süresi 27 aydı. Tüm hastalarda remisyona ulaşıldı (ortanca yanıt süresi: 62 gün), ancak %36,4'ünde nüks görüldü. Yüksek inhibitör titresi (>20 Bethesda ünitesi) gecikmiş yanıtla (p=0,038); erkek cinsiyet ve majör kanama daha kısa nükssüz sağkalımla ilişkilendirildi. Tanıdaki inhibitör yükü ve hastalık etiyolojisi EHA prognozunu etkilemektedir. Yönetim stratejilerini iyileştirmek için kişiselleştirilmiş tedavi ve çok merkezli validasyon gereklidir.

Anahtar Sözcükler: Edinsel hemofili A, Kanama bozukluğu, İnhibitör, Bypass ajanları, İmmünosüpresif tedavi

Introduction

Acquired hemophilia A (AHA) is a rare autoimmune bleeding disorder caused by autoantibodies against factor VIII (FVIII). It typically affects older adults but may occur postpartum [1,2]. Its incidence is approximately 1.5 per million annually [3]. Its management involves prompt diagnosis, bleeding control with bypassing agents, immunosuppressive therapy (IST) for inhibitor eradication, and evaluation for underlying conditions to guide treatment [1,4,5].

We conducted a single-center retrospective study to assess clinical features, treatment modalities, and outcomes in adult AHA patients, focusing on prognostic indicators affecting treatment response, relapse, and survival.

Materials and Methods

Our study included patients aged ≥18 years diagnosed with AHA at the Cerrahpaşa Faculty of Medicine (İstanbul, Türkiye) between January 2008 and December 2024 based

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Received/Geliş tarihi: May 24, 2025
Accepted/Kabul tarihi: August 26, 2025
Epub: August 27, 2025

on international criteria [6]. Ethical approval was from the İstanbul University–Cerrahpaşa Ethics Committee (date: 05-03-2025, no: 2025/156). Data on demographics, bleeding features, comorbidities, FVIII activity, inhibitor titers, treatments, and outcomes were retrospectively collected.

Major bleeding was defined by involvement of vital organs, hemoglobin drop of ≥2 g/dL, or ≥2 units of red blood cell transfusion; other bleeding events were classified as minor. Response definitions followed the published guidelines [7]. The follow-up period was defined as the time from diagnosis to last visit or death.

Statistical Analysis

Categorical variables were compared using chi-square or Fisher exact tests. The Mann-Whitney U test was applied for non-parametric continuous variables. Kaplan-Meier estimates were used for overall survival (OS) and relapse-free survival (RFS).

Results

Eleven patients (54.5% female) with a median age of 41 (range: 26-79) years were analyzed. In 36.3% cases, no underlying cause was found; the postpartum period was the most common identifiable etiology (Table 1). Three patients had connective tissue disorders (bullous pemphigoid or rheumatoid arthritis) (Tables 1 and 2).

FVIII activity was <1% in 81.8% cases and inhibitor titers were >20 Bethesda units per milliliter (BU/mL) in 63.6%. All patients presented with bleeding, with 45.4% having major hemorrhages (Table 1).

Patient characteristics, treatment approaches, and disease course were summarized in Table 2. Recombinant activated factor VII (rFVIIa) and activated prothrombin complex concentrate (aPCC) were used in six cases each to control the initial bleeding episode, accounting for 81.8% of the cohort. Combinations of or switches between agents occurred in three cases. Desmopressin, high-dose FVIII, and emicizumab were not used. One patient underwent plasmapheresis and right femoral artery embolization (Table 2).

The median hemostasis duration was 7 (range: 2-45) days. Patients with minor bleeding had shorter bypassing agent use (p=0.027). The number of bleeding sites did not significantly affect hemostasis duration (p=0.47).

All patients received IST. Steroid monotherapy was the first-line treatment in 90.9% of cases (Table 2). Due to regulatory delays in Türkiye, first-line use of rituximab is often impossible. In our center, rituximab is usually added to corticosteroid therapy for patients who fail to respond to first-line steroid monotherapy or who have recurrent clinical bleeding and/or prolongation of activated partial thromboplastin time (APTT) during steroid tapering after an initial response.

Three patients (all pregnancy-associated cases) with inhibitor titers of ≤20 BU achieved complete remission (CR) with steroids alone, without relapse. A fourth postpartum case with inhibitor titer of >20 BU also achieved CR with added rituximab (Table 2).

Of the three patients with autoimmune disorder-associated AHA, one achieved CR with cyclophosphamide, whereas two required the addition of rituximab to steroid monotherapy. One of these patients relapsed and was successfully re-treated (Table 2). Among the idiopathic AHA cases (36.3%), only one patient sustained CR with steroids alone. The remaining three initially responded to combination therapy but relapse occurred in two of them (Table 2).

Table 1. Demographic and clinical characteristics of patients.

Parameter	Total (n=11)
Sex, n (%)	
Female	6 (54.5)
Male	5 (45.5)
Age at diagnosis, years	
Median (range)	41 (26-79)
Age categories, n (%)	
≤70 years	8 (72.7)
>70 years	3 (27.3)
Underlying disorder	
Idiopathic/none	4 (36.3)
Connective tissue disorders	3 (27.3)
Pregnancy	4 (36.3)
Hemoglobin level at diagnosis (g/dL)	
Median (range)	11.7 (5.8-14.7)
APTT at diagnosis (s)	
Median (range)	82 (53.9-121)
FVIII level at diagnosis (IU/dL)	
Median (range)	0.6 (0.1-5)
FVIII inhibitor titer at diagnosis (BU/mL)	
Median (range)	36.95 (2-130)
Severity of bleeding at diagnosis, n (%)	
Major	5 (45.4)
Minor	6 (54.5)
Number of bleeding sites at diagnosis, n (%)	
1	3 (27.2)
≥2	8 (72.7)
Number of bleeding sites (all), n (%)	
Skin and subcutaneous tissue	8 (72.7)
Joint	2 (18.1)
Muscle	5 (45.4)
Gastrointestinal system	1 (9)
Genitourinary system	3 (27.2)

APTT: Activated partial thromboplastin time; FVIII: factor VIII; BU: Bethesda unit.

Table 2. Clinical features, treatments, and outcomes in acquired hemophilia A patients.

Patient no.	Age at Dx, sex	Underlying disorder	Inh titer (BU/mL)	Major/ minor bleeding	Bypassing agent used	IST	Time to achieve CR (days)	Duration until relapse	Second-line bypassing agent choice	Second and subsequent IST	Treatment response	Follow-up duration (months)
1¥	77, F	Bullous pemphigoid	60	Major	rFVIIa rFVIIa + aPCC	CTX	140	None				15
2	41, M	Idiopathic	104	Major	rFVIIa	MP	160	2 months	rFVIIa + aPCC	MP + CTX CTX RTX	No response	173
3	30, F	Postpartum period	2	Minor	None	MP	60	None				27
4	56, M	Idiopathic	78	Major	aPCC rFVIIa	MP + CTX	150	50 months	aPCC	MP + RTX MP + RTX	No response	116
5	26, F	Postpartum period	32	Minor	aPCC	MP + RTX	60	None				19
6¥	78, M	Bullous pemphigoid	40	Major	aPCC Plasmapheresis Embolization	MP + RTX	48	1 month	aPCC	MP + CTX	CR	11
7	34, F	Idiopathic	34	Minor	aPCC	MP + CTX	160	None				24
8	39, F	Postpartum period	3	Minor	rFVIIa	MP	44	None				35
9	41, F	Postpartum period	2	Minor	aPCC rFVIIa	MP	44	None				51
10	54, M	Idiopathic	NA	Major	rFVIIa	MP + RTX	78	18 months	rFVIIa	MP + RTX	CR	36
11	77, M	Rheumatoid arthritis	130	Minor	None	MP + RTX	62	None				3

¥: Patient deceased; aPCC: activated prothrombin complex concentrate; BU: Bethesda unit; CR: complete remission; CTX: cyclophosphamide; Dx: diagnosis; F: female; IST: immunosuppressive therapy; Inh: inhibitor; M: male; MP: methylprednisolone; rFVIIa: recombinant activated factor VII; RTX: rituximab.

All patients achieved CR with a median time of 62 (range: 44-160) days. Inhibitor titer of >20 BU was associated with longer time to CR (p=0.038). Pregnancy-associated cases had significantly shorter time to CR (p=0.022), whereas idiopathic cases required longer periods of time to reach CR (p=0.013). Baseline FVIII activity and bleeding severity were not significantly associated with treatment duration (p=0.075 and p=0.168, respectively). There was no significant relationship between the type of bypassing agent used and time to remission (p=0.783).

Median follow-up was 27 months (range: 3-173). Four patients (36.4%) experienced relapse; two of them had multiple relapses without sustained response (Table 2). One patient (Patient #4) developed popliteal vein thrombosis during relapse while receiving aPCC. Two patients (Patients #1 and #6) died, one from trauma-induced hemorrhage and the other from unknown causes.

In univariate analysis, male sex and major bleeding at presentation were associated with shorter RFS (p=0.015 for both). No factor reached significance for survival, although age of >50 years, hemoglobin of <10 g/dL, and non-pregnancy-associated AHA trended toward significance (p=0.062). Inhibitor titer, APTT, and type of bypassing agent were not predictive for either RFS or OS (Table 3).

Discussion

AHA is a rare and serious bleeding disorder caused by neutralizing autoantibodies against FVIII, requiring prompt diagnosis. The management of AHA involves both the control of acute bleeding episodes and the eradication of inhibitors through IST [1,8]. Our single-center study provides valuable insights into the clinical characteristics, treatment responses, and outcomes of patients with AHA, thereby contributing to the current understanding of this uncommon condition.

In our cohort, bypassing agents were administered for 77.8% of patients to achieve bleeding control, consistent with the EACH2 registry (70.5%) [9]. Both rFVIIa

Table 3. Factors affecting relapse-free survival and overall survival in acquired hemophilia A.

Variable	RFS p value	OS p value
Age at diagnosis of >50 years	0.161	0.062
Male sex	**0.015**	0.695
Major bleeding at diagnosis	**0.015**	0.134
≥2 bleeding sites	0.273	0.464
Non-pregnancy-associated cases	0.062	0.226
Idiopathic cases	0.183	0.226
APTT of >100 s	0.273	0.577
Factor VIII of >1 IU/dL	0.923	0.176
Inhibitor titer of >20 BU/mL	0.17	0.295
Hemoglobin of <10 g/dL	0.06	0.062
Use of bypassing agents	0.424	0.627
Use of aPCC	0.474	0.226
Use of recombinant factor VIIa	0.741	0.695

aPCC: Activated prothrombin complex concentrate; APTT: activated partial thromboplastin time; BU: Bethesda unit; OS: overall survival; RFS: relapse-free survival.

and aPCC were effective, aligning with prior studies reporting 80%-90% efficacy [10].

Currently, no laboratory parameters reliably predict or monitor the efficacy of bypassing agents; thus, treatment response must be evaluated clinically [1]. This limitation can create uncertainty regarding the optimal duration of therapy. One patient developed popliteal vein thrombosis while receiving aPCC, underscoring the need for thrombotic risk monitoring, especially when agents are combined.

Steroid monotherapy was the initial IST in 90.9% of cases and all of these patients achieved CR, with a median response time of 62 days, slightly longer than the timeframe of 5-6 weeks reported in previous cohorts [3,8,9]. In the EACH2 registry [9] and the study by Lindahl et al. [11], corticosteroid monotherapy yielded CR rates of 57%-72%, whereas regimens incorporating rituximab achieved CR rates up to 90% [8]. In our cohort, four patients received rituximab as first-line therapy and all four achieved CR.

Pregnancy-associated AHA, accounting for 36.4% of cases, showed a particularly favorable course: three of four patients responded to steroids alone and none experienced relapse. These patients had significantly shorter response times (p=0.022) and lower inhibitor titers, supporting previously reported data suggesting a transient, self-limiting postpartum immune dysregulation [3,6,12]. In contrast, idiopathic and autoimmune-associated cases more often required combination IST and showed higher relapse rates and delayed remission (p=0.013).

A high inhibitor titer (>20 BU) was significantly associated with delayed IST response (p=0.038), consistent with previous studies demonstrating that higher inhibitor levels are linked to a more protracted treatment course [7,13,14]. Neither FVIII activity of >1% nor initial bleeding severity predicted time to remission.

Relapse occurred in 36.4% of cases, a rate higher than that of 14% reported by Lindahl et al. [11]. This may reflect early IST tapering or discontinuation. Additionally, patients with multiple relapses posed treatment challenges, highlighting the need for alternative or intensified IST strategies in refractory cases.

Compared to the only previous multicenter AHA study from Türkiye [15,16], our cohort had comparable initial characteristics but higher aPCC utilization, longer median follow-up, and a higher relapse rate.

Conclusion

Limitations of this study include the retrospective design and small sample size. However, our study underscores the clinical heterogeneity of AHA and highlights the prognostic significance of baseline inhibitor titers and underlying disease etiology. Individualized treatment approaches are crucial, particularly for high-risk subgroups. Larger multicenter studies are needed to validate prognostic markers and optimize therapeutic strategies for sustained remission and reduced complications.

Ethics

Ethics Committee Approval: Ethical approval was from the İstanbul University–Cerrahpaşa Ethics Committee (date: 05-03-2025, no: 2025/156).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.K.K., U.Y., T.E., Z.B., M.C.A.; Concept: S.K.K., M.C.A.; Design: S.K.K., M.C.A.; Data Collection or Processing: S.K.K., P.Ö., U.Y., D.S.E., M.C.A.; Analysis or Interpretation: S.K.K., M.C.A.; Literature Search: S.K.K., M.C.A.; Writing: S.K.K., M.C.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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