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ORIGINAL ARTICLE

Acquired hemophilia A: a single-center study of 165 patients

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Abstract

Background: Acquired hemophilia A (AHA) is a rare hemorrhagic disorder caused by factor (F)VIII inhibitors. The diagnosis and management of AHA remains challenging because of its rarity and heterogeneity.

Objectives: To analyze the characteristics of AHA to enhance our understanding of this disease and identify effective treatment strategies. To analyze the characteristics of AHA to enhance our understanding of this disease and identify effective treatment strategies.

Methods: Clinical features of 165 patients with AHA from a single center between July 1997 and December 2021 were retrospectively analyzed.

Results: The median age of patients at diagnosis was 45 years. The median time to diagnosis was 30 days. All 165 patients experienced bleeding, with a median bleeding score (BS) of 4 (range, 2-12). Hemostatic therapy was administered to 129 (78.2%) patients. Bleeding control was achieved in 80.0% of patients who received prothrombin complex concentrate and in 92.3% of patients who were treated with recombinant activated FVII. Of the 163 patients who received immunosuppressive therapy, 80 (49.1%) received rituximab-based therapy with a 93.3% complete remission (CR) rate, 50 (30.7%) received steroids plus cyclophosphamide with an 85.0% CR rate, and 22 (13.5%) received steroids alone with an 82.4% CR rate. Six cases relapsed after a median duration of 330 days. Immunosuppressive therapy–related adverse events were reported in 17 patients. Seven deaths were recorded. FVIII inhibitor titer of ≥15 BU/mL and BS of ≥6 were identified as significantly poor prognostic factors for CR.

Conclusion: Immunosuppressive therapies yield remarkably high response rates, with a CR rate exceeding 80%; notably, the regimen containing rituximab exhibits a CR rate of approximately 90%. FVIII inhibitor titer of ≥5 BU/mL and BS of ≥6 were poor predictors of CR in patients with AHA.

KEYWORDS
acquired hemophilia A, bleeding, immunosuppression, inhibitor, prognosis

Essentials

- Acquired hemophilia A is a rare bleeding disorder due to factor VIII inhibitors.
- Clinical features of 165 patients with acquired hemophilia A from a single center were retrospectively analyzed.
- Complete remission rate of rituximab-based regimens was approximately 90%.
- FVIII inhibitor titer of ≥15 BU/mL and bleeding score of ≥6 were poor predictors of complete remission.

1 | INTRODUCTION

Acquired hemophilia A (AHA) is a rare bleeding disorder caused by antibodies directly neutralizing factor (F)VIII. The estimated annual incidence is 1.5 per million people [1]. The incidence rates tend to increase with age, exhibiting 2 age peaks: (1) among women of childbearing age and (2) in older adults (age ≥ 60 years) [2,3]. About half of the patients with AHA have underlying conditions, which are mainly autoimmune diseases, malignancies, infections, and pregnancy [4]. AHA is characterized by excessive bleeding episodes that occur spontaneously or after trauma or surgery in individuals without a previous history of bleeding. Approximately 10% of patients with AHA have no bleeding symptoms [5]. In contrast to patients with congenital hemophilia A, hemarthrosis is less common in patients with AHA, and subcutaneous hemorrhage occurs more frequently in these patients [6]. Patients with AHA typically exhibit isolated prolonged activated partial thromboplastin time (aPTT) due to FVIII deficiency, along with positivity for FVIII inhibitors. Prompt intervention to control bleeding and eliminate inhibitors following diagnosis is critical for effective treatment in patients with AHA.

However, the lack of awareness of AHA and the inability to perform coagulation laboratory assays, including the Bethesda assay in clinics, may preclude early diagnosis of AHA and result in serious complications in patients with AHA. Given the rarity of AHA, large-scale studies remain scarce. Therefore, we conducted a retrospective study to evaluate the clinical characteristics, treatments, and outcomes of AHA to better understand this disease and identify effective treatment strategies.

2 | METHODS

2.1 | Patients

Patients diagnosed and treated with AHA at the Blood Disease Hospital, Chinese Academy of Medical Sciences, between July 1997 and December 2021, were enrolled retrospectively by searching our institution's electronic medical record system. The inclusion criteria were as follows: (1) acquired FVIII deficiency, (2) FVIII level below the normal limits (<50 IU/dL) (reference value, 50-100 IU/dL, which was set by our laboratory based on local conditions), and (3) FVIII inhibitor titer ≥ 0.6 BU/mL. The exclusion criteria were as follows: (1) congenital FVIII deficiency, (2) positive lupus anticoagulant, and (3) acquired von Willebrand factor deficiency. Data regarding demographics, comorbidities, clinical characteristics, treatments, outcomes, and adverse events (AEs) were retrospectively collected.

All patients were followed up immediately from admission at our center until March 2022. Factor activity and inhibitor level tests were conducted weekly until complete remission (CR) was achieved. Subsequently, these tests were repeated at 3, 6, 12, and 18 months after CR, followed by annual assessments or assessments whenever bleeding episodes occurred. AEs and associated tests were monitored weekly until the completion of immunosuppressive therapy (IST) within 8 weeks. In cases where patients were unable to attend regular hospital visits, telephone follow-ups were conducted to document the timing and results of their last assessment. The patients whose status remained unknown at the last follow-up were categorized as "lost to follow-up."

Bleeding severity was assessed retrospectively in March 2022 using bleeding score (BS) based on the medical history. The BS is a summary score aggregated by the International Society on Thrombosis and Hemostasis/Scientific and Standardization Committee Bleeding Assessment Tool (2010 edition) [7]. The normal range of BS is 0 to 5 for adult females, 0 to 3 for adult males, and 0 to 2 for children [8].

The primary endpoint was CR, which was defined as a normal FVIII level (≥50 IU/dL) and undetectable FVIII inhibitor (<0.6 BU/mL). The secondary endpoint was partial remission (PR), relapse, time to PR, time to CR, and time to relapse. PR was defined as a normal FVIII activity (≥50 IU/dL) but the persistence of positive FVIII inhibitor (≥0.6 BU/mL). Relapse was defined as the FVIII level dropping below 50 IU/dL and the reoccurrence of FVIII inhibitor (≥0.6 BU/mL) after CR [9,10]. Time to CR/PR was defined as the number of days from the start of regular IST to the achievement of CR/PR. Time to relapse was defined as the time from achieving CR to relapse.

2.2 | Laboratory tests

Our clinic has used a uniform coagulation testing protocol over the past 25 years. Coagulation assays, including aPTT, aPTT mixing test, FVIII level assay, and FVIII inhibitor assay, were performed for each patient. The aPTT mixing test was used as a screening step to detect the presence of FVIII inhibitors. In brief, the patient's plasma was mixed with normal plasma in a 1:1 ratio; subsequently, aPTT was determined immediately and after 2 hours of incubation at 37 °C. The mixing test was considered positive when prolonged aPTT was not corrected [11]. FVIII level assay was conducted using a 1-stage aPTT-

based assay. FVIII inhibitors were quantified using the Bethesda method based on FVIII activity testing. When the FVIII activity was >5%, a heat inactivation treatment step was implemented by heating plasma samples at 56 °C for 30 minutes before conducting FVIII inhibitor assays [12]. (The comprehensive laboratory methods are provided in the Supplementary Methods).

2.3 | Statistical analysis

The Mann–Whitney U-test was performed to compare continuous variables, and the chi-squared test or Kruskal–Wallis rank test was conducted for categorical variables. Correlations between continuous variables were assessed using Spearman correlation test. The time to achieve CR, treated as an event, was analyzed using the Kaplan–Meier method and log-rank test. Patients whose status was unavailable at the last follow-up were treated as censored data in the analysis. Finally, univariate and multivariate Cox regression analyses were performed to compare the differences in time to CR based on binary variables such as age, underlying illnesses, BS, factor activity, and factor inhibitor titer. Hazard ratios (HRs) were used to determine the time to CR.

Statistical significance was set at $P < .05$. All analyses were performed using R software, version 4.1.2 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Demographics

From July 1997 to December 2021, 165 patients with AHA admitted to our center were enrolled. The baseline characteristics of all patients are shown in Table 1. The median age at diagnosis of the overall cohort was 45 (range, 10-90) years, with 29.7% (49/165) of individuals aged over 60 years. Overall, female predominance (106/165, 64.2%) was observed in this cohort, especially in individuals aged 20 to 37 years, of whom females accounted for 73.2% (41/56). The proportion of male patients increased with age. Among younger patients (<20 years), males comprised 25.0% (2/8), while among older patients (≥60 years), males represented 55.1% (27/49).

Most patients (126/165, 76.4%) were idiopathic. Of the 39 (23.6%) patients with associated diseases, 12 (7.3%) had autoimmune diseases, 16 (9.7%) had infections, 8 (4.8%) had malignancies (all solid tumors), and 3 (1.8%) had pregnancy. The characteristics of patients with idiopathic AHA and those with associated diseases are shown in Supplementary Table S1. Compared with patients with idiopathic AHA, a higher proportion of female and older patients (age ≥ 60 years) were observed in patients with associated conditions, although the difference was not statistically significant ($P > .05$).

TABLE 1 Baseline characteristics of patients with acquired hemophilia A at diagnosis.

Characteristics	Patients, *n* (%)	Sex (male/female), *n* (%)
All	165 (100.0)	59 (35.8)/106 (64.2)
Age (y)		
<20	8 (4.8)	2 (25.0)/6 (75.0)
20-40	61 (40.0)	15 (24.6)/46 (75.6)
40-60	47 (28.5)	15 (31.9)/32 (68.1)
≥60	49 (29.7)	27 (55.1)/22 (44.9)
Underlying diseases		
None/idiopathic	126 (76.4)	45 (35.7)/81 (64.3)
Autoimmune disease	12 (7.3)	3 (25.0)/9 (75.0)
Malignancy	8 (4.8)	5 (62.5)/3 (37.5)
Infection	16 (9.7)	6 (37.5)/10 (62.5)
Pregnancy	3 (1.8)	0 (0.0)/3 (100.0)
FVIII level (IU/dL)		
≤1	81 (49.1)	34 (42.0)/47 (58.0)
1-5	72 (43.6)	21 (29.2)/51 (70.8)
5-50	12 (7.3)	4 (33.3)/8 (66.7)
FVIII inhibitor titer (BU/mL)		
<20	102 (61.8)	28 (27.5)/74 (72.5)
≥20	63 (38.2)	31 (49.2)/32 (50.8)
Bleeding presentation		
Ecchymosis	140 (84.8)	-
Hematuria	45 (27.3)	-
Muscle hemorrhage	30 (18.2)	-
Oral mucosal hematoma	23 (13.9)	-
Menorrhagia	3 (1.8)	-
Epistaxis	3 (1.8)	-
Hemarthrosis	11 (6.7)	-
Gingival bleeding	9 (5.5)	-
Postoperative hemorrhage	5 (3.0)	-
Other	11 (6.7)	-
No bleeding	0 (0.0)	-

F, factor.

3.2 | Laboratory tests

About half of the patients (81/165, 49.1%) had severe FVIII deficiency (FVIII:C ≤ 1 IU/dL), and 7.3% (12/165) of patients had mild FVIII deficiency (FVIII:C > 5 IU/dL). The proportion of patients with low FVIII inhibitor titer (<15 BU/mL) was 47.3%, and 52.7% had high FVIII inhibitor titer (≥15 BU/mL). The FVIII inhibitor titer and FVIII level showed no correlation (Figure 1A). A significant difference in FVIII

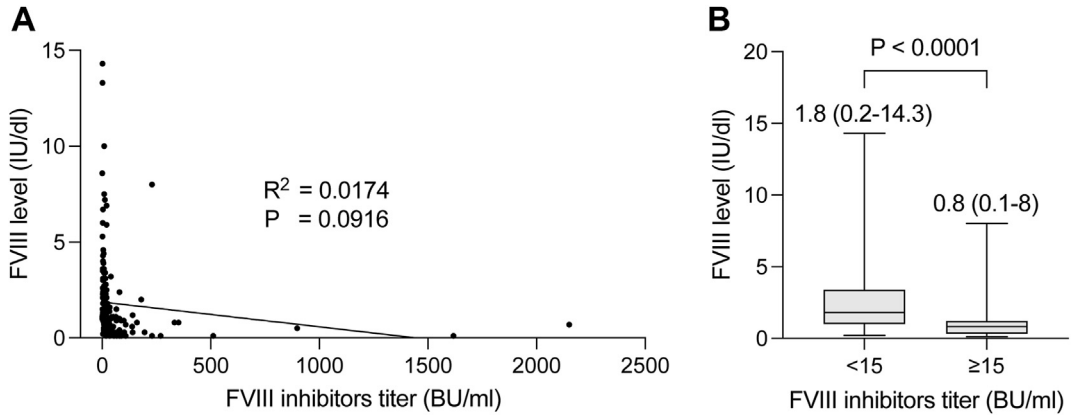

FIGURE 1 Analysis of factor (F)VIII level and FVIII inhibitor titer of all patients with acquired hemophilia A. (A) FVIII level and FVIII inhibitor titer analysis using linear regression. (B) The median FVIII level of patients with FVIII inhibitor titer < 15 BU/mL and ≥ 15 BU/mL is depicted by the box and whisker plots.

activity was observed between patients with FVIII inhibitor titer < 15 BU/mL and ≥ 15 BU/mL ($P < .05$) (Figure 1B).

3.3 | Bleeding presentations

All 165 patients presented with at least 1 bleeding episode. The diverse bleeding phenotypes are shown in Table 1. Subcutaneous bleeding was the most prevalent manifestation, affecting 84.8% (140/165) of patients, while hemarthrosis occurred infrequently, affecting only 6.7% (11/165) of patients.

The BS varied among the patients, with a median value of 4 (range, 2-12). A significant difference in BS was observed among patients with mild (FVIII:C > 5 IU/dL), moderate (1 IU/dL < FVIII:C ≤ 5 IU/dL), and severe (FVIII:C ≤ 1 IU/dL) FVIII deficiency ($P < .05$) (Figure 2A). No noteworthy distinction in BS was discerned between patients with low FVIII inhibitor titer (<15 BU/mL) and those with high FVIII inhibitor titer (≥15 BU/mL) (Figure 2B). BS was not correlated with aPTT ($r = -0.04$; 95% CI, −0.19 to 0.12; $P > .05$). Although the BS of patients with idiopathic AHA was lower than that of patients with associated conditions (4 vs 5), no statistically significant difference was observed between the 2 groups ($P > .05$) (Supplementary Table S1).

3.4 | Diagnosis

All 165 patients sought consultation due to bleeding events. In the overall cohort, the median time from the onset of bleeding to the diagnosis of AHA was 30 (2-5650) days. Only 11 (6.6%) patients sought immediate medical attention at our hospital after their first bleeding events, with a median time to diagnosis of 10 (4-30) days.

In contrast, 85 (51.5%) patients sought consultation at multiple hospitals without receiving a clear diagnosis until they were transferred to our center, resulting in a median time to diagnosis of 30 (10-5650) days. Additionally, another 69 (41.8%) patients were transferred to our hospital for further treatment owing to

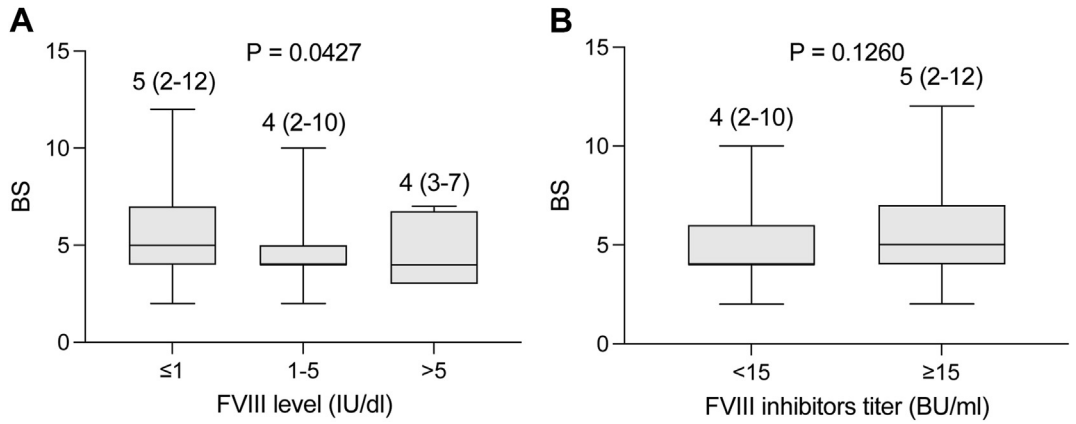

FIGURE 2 The median bleeding score (BS) of patients with acquired hemophilia A with different factor (F)VIII levels and different FVIII inhibitor titer. (A) The box and whisker plots depict the median BS of patients with FVIII level ≤ 1 IU/dL, 1 IU/dL < FVIII level ≤ 5 IU/dL, and FVIII level > 5 IU/dL. (B) The box and whisker plots depict the median BS of patients with FVIII inhibitor titer < 15 BU/mL and ≥ 15 BU/mL.

unsatisfactory treatment outcomes after a confirmed diagnosis at other hospitals; the median time to diagnosis was 30 (10-1100) days.

3.5 | Hemostatic therapy

Given the unavailability of activated prothrombin complex concentrate in China, 4-factor prothrombin complex concentrate (PCC) containing nonactivated FII, FVII, FIX, and FX has been used as an alternative to hemostatic agents. Hemostatic treatment was administered to 129 (78.2%) patients, of whom 29 (22.5%) received only fresh frozen plasma (FFP) or cryoprecipitate (CP) at other health care facilities before admission to our center. PCC, recombinant activated FVII (rFVIIa), and FVIII concentrates were administered to 83 (64.3%), 13 (10.1%), and 30 (23.3%) patients, respectively. Only 1 patient was administered aminocaproic acid as an adjuvant hemostatic agent. Some patients (36/165, 21.8%) presented with mild subcutaneous bleeding, for which no specific hemostatic treatment was administered.

An overview of the hemostatic therapy protocols employed for patients at our center is shown in Supplementary Table S2. FFP and CP were ineffective in achieving hemostasis, prompting the administration of alternative hemostatic agents for bleeding control. Consequently, the hemostatic efficacy of FFP and CP could not be evaluated in this context.

Bleeding control was achieved in 46 of 50 patients (80.0%) who received PCC alone. In the 4 patients who did not initially respond to PCC, bleeding was successfully resolved after receiving 1 to 2 doses of rFVIIa treatment. Most patients (12/13, 92.3%) who received rFVIIa achieved hemostasis. The resolution of bleeding was assessed at 8- to 12-hour intervals after the administration of hemostatic therapy. Specifically, the median time to bleeding cessation was 8 hours for patients receiving rFVIIa and 60 hours for those receiving PCC treatment (Supplementary Table S2).

Three patients were administered FVIII to manage bleeding. The bleeding symptom was improved in 1 patient with a single dose of 18.2 IU/kg (total 1200 IU) of FVIII. Another patient initially received a single dose of 2.7 IU/kg (total 200 IU) of FVIII but continued to experience bleeding. After 24 hours, she was administered PCC at a dose of 27.4 IU/kg (total 2000 IU) per day for 2 days, which achieved hemostasis. The third patient achieved hemostasis after receiving 55.6 IU/kg (total 5000 IU) of FVIII following an ineffective response to rFVIIa and PCC.

3.6 | Immunosuppressive therapy and outcome

A total of 163 patients at our center received IST to eradicate inhibitors (Table 2). The most commonly employed IST was rituximab-based (80/163, 49.1%) regimens, including rituximab combined with steroids, steroids and cyclophosphamide (CTX), or other immunosuppressants. Fifty (30.7%) patients received a combination of steroids and CTX, and 22 (13.5%) were administered steroids alone. Among patients with idiopathic AHA, the rituximab-based regimen was the predominant treatment choice (69/126, 54.8%). Conversely, among patients with associated conditions, the number of cases using the rituximab-based regimen, steroids combined with CTX, and steroids alone was approximately equal (Supplementary Table S1). One patient died of intracranial hemorrhage immediately after admission to our center without receiving IST. Another patient was diagnosed at our center and was subsequently discharged without IST.

The outcome of 136 of 163 patients receiving IST was recorded; 125 (91.9%) achieved PR, and 120 (88.2%) achieved CR (Table 2). The median time to achieve PR and CR in all patients receiving IST was 40 (17-63) and 57 (21-98) days, respectively. Patients treated with the rituximab-based regimen achieved the highest CR rate (93.3%), followed by those receiving steroids combined with CTX (85.0%) and those receiving steroids alone (82.4%) ($P < .05$) (Figure 3A).

TABLE 2 Response to first-line immunosuppressive therapy of patients with acquired hemophilia A.

Treatment	Patients treated, *n*	Patients with recorded outcome, *n*	PR, *n* (%)	Initial CR, *n* (%)				Relapse, *n* (%)	Stable CR, *n* (%)	Dead, *n* (%)	Causes of death
				Total	Ab titers <15 BU/mL	Ab titers ≥15 BU/mL	*P* value				
Steroids alone	22	17	15 (88.2)	14 (82.4)	8/9 (88.8)	6/8 (75.0)	.45	1 (7.1)	13 (76.5)	2 (11.8)	Bleeding
Steroids + CTX	50	40	37 (92.5)	34 (85.0)	21/22 (95.5)	13/18 (72.2)	.07	1 (2.9)	33 (82.5)	2 (5.0)	Underlying disease, bleeding
RTX-based[a]	80	75	71 (94.7)	70 (93.3)	35/36 (97.2)	35/39 (89.7)	.36	4 (5.7)	66 (88.0)	1 (1.3)	Pulmonary infection
Others[b]	11	4	2 (50.0)	2 (50.0)	1/2 (50.0)	1/2 (50.0)	-	0 (0.0)	2 (50.0)	1 (25.0)	Bleeding
No treatment	2	1	0 (0.0)	0 (0.0)	0/0 (0.0)	0/1 (0.0)	-	0 (0.0)	0 (0.0)	1 (100.0)	Bleeding
Total	**165**	**137**	**125 (91.2)**	**120 (87.6)**	**65/69 (94.2)**	**55/68 (80.1)**	<.05	**6 (5.0)**	**114 (83.2)**	**7 (5.1)**	

Ab, antibody; CR, complete remission; CTX, cyclophosphamide; PR, partial remission; RTX, rituximab.

[a]RTX-based: RTX + steroids, RTX + steroids + CTX, RTX + steroids + others.

[b]Others: steroids + CTX + azathioprine, steroids + CTX + cyclosporin A, steroids + CTX + bortezomib.

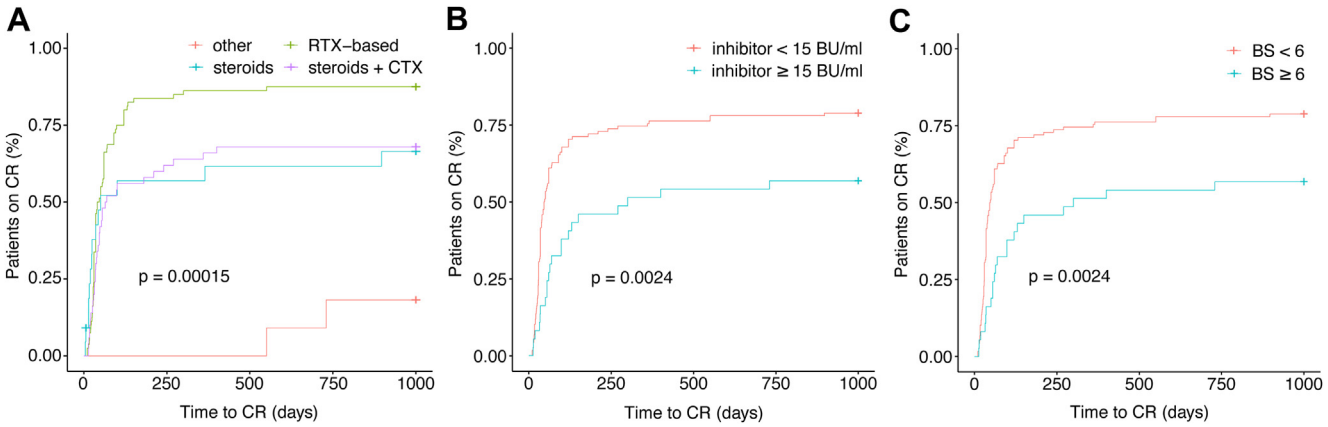

FIGURE 3 Outcomes according to immunosuppressive therapy, factor (F)VIII inhibitor titer, and bleeding score (BS). (A) Kaplan–Meier curves describing the complete remission (CR) rate of patients with acquired hemophilia A (AHA) with variable immunosuppressive therapy. (B) Kaplan–Meier curves showing the CR rate of patients with AHA with FVIII inhibitor titer < 15 BU/mL and ≥ 15 BU/mL. (C) Kaplan–Meier curves describing the CR rate of patients with AHA with BS < 6 and ≥ 6. CTX, cyclophosphamide; RTX, rituximab.

The median time to achieve CR among patients receiving the rituximab-based regimen, steroids combined with CTX, and steroids alone was 40, 46, and 60 days, respectively. Furthermore, patients with idiopathic AHA exhibited a higher CR rate than those with associated diseases (81.7% vs 43.6%, $P < .05$) (Supplementary Table S1).

Six (6/120, 5.0%) relapsed cases occurred in patients who had achieved CR, yielding a stable CR rate of 83.8% (114/136). Four patients relapsed with the rituximab-based regimen (3, 3, 10, and 16 months after CR), 1 patient relapsed with the combination of steroids and CTX (120 months after CR), and 1 patient relapsed with steroids alone (12 months after CR). The median time to relapse was 330 (90-3600) days.

3.7 | AEs

IST-related AEs were reported in 17 patients. The types of AEs and the time intervals from the initiation of immunosuppression to their occurrence were as follows: 11 cases of pulmonary infections (1, 2, 2, 8, and 8 weeks after intravenous [i.v.] infusion of rituximab; 8, 10, 14, and 14 days after i.v. infusion of CTX; and 9 and 20 days after oral steroids alone), 2 cases of leucopenia (4 and 20 days after i.v. infusion of CTX), 2 cases of thrombocytopenia (1 month after i.v. infusion of bortezomib and 3 months after oral zanubrutinib), 1 case of elevated transaminases (18 days after i.v. infusion of CTX), and 1 case of hyperglycemia (1 week after oral steroids alone). Most patients recovered with or without treatment, except 1 who received the rituximab-based regimen and died due to severe pneumonia. No thrombotic events were observed in this cohort.

3.8 | Follow-up and outcome

The survival outcomes were recorded in 137 patients at the last follow-up. Seven (5.1%) patients died in the total cohort. Five patients died after discharge; 1 died due to tumor recurrence and the remaining 4 died due to severe bleeding following ineffective IST. Overall, patients with associated diseases exhibited a significantly higher mortality rate than those with idiopathic AHA (12.8% vs 1.6%, $P < .05$) (Supplementary Table S1).

3.9 | Prognostic factors for remission

We performed analyses to identify the factors affecting CR in patients with AHA. FVIII inhibitor titer ≥ 15 BU/mL (HR, 0.55; 95% CI, 0.37-0.82; $P < .05$) and BS ≥ 6 (HR, 0.54; 95% CI, 0.33-0.89; $P < .05$) were significantly poor prognostic factors for CR (Table 3). In addition, patients with FVIII inhibitor titer ≥ 15 BU/mL needed more time to achieve CR (60 days vs 30 days, $P < .05$) and showed a lower CR rate (80.1% vs 94.2%, $P < .05$) than those with FVIII inhibitor titer < 15 BU/mL (Table 2 and Figure 3B). Patients with BS ≥ 6 needed more

TABLE 3 Predictors of time to achieve complete remission in patients in multivariate Cox regression analysis.

	Time to CR	
Baseline variables	**Hazard ratio (95% CI)**	***P* value**
Age ≥ 60 y	0.65 (0.39-1.09)	.10
Secondary cases	0.97 (0.54-1.74)	.907
BS ≥ 6	0.54 (0.33-0.89)	.015
Inhibitor titer ≥ 15 BU/mL	0.55 (0.37-0.82)	.003
FVIII activity ≥ 1 IU/dL	1.17 (0.78-21.75)	.45
First IST:RTX-based[a]	1.61 (1.05-2.48)	.03

BS, bleeding score; CR, complete remission; F, factor; IST, immunosuppressive therapy; RTX, rituximab.
[a]RTX-based: RTX + steroids, RTX + steroids + CTX, RTX + steroids + others.

time to achieve CR (70 days vs 40 days, $P < .05$) and showed a lower CR rate (78.0% vs 93.1%, $P < .05$) than those with BS < 6.

4 | DISCUSSION

This study comprehensively analyzed the clinical features and outcomes of 165 patients with AHA over the past 25 years at a single center. To some extent, the study population reflects the demographic characteristics and current state of AHA diagnosis and management in China. Our specialized hematology center may exhibit a propensity to achieve more favorable outcomes in the diagnosis and management of this condition.

The median age at diagnosis of the patients in our sample was 45 years, which is lower than that reported in previous studies from Western countries (64-78 years) [3,13,14]. This disparity can be partly attributed to the distinct age dynamics observed in patients with AHA across different geographic areas. Our study participants exclusively consist of individuals from China, all of whom identify with the Asian ethnicity. Data from the China Acquired Hemophilia Registry (CARE) [10] showed a younger patient demographic (52 years), similar to our findings. Furthermore, a separate study underscored the consistently younger demographic characteristics of patients with AHA (58 years) in Asian countries [15]. The difference may also be interpreted in part by referral bias. Compared with older patients, younger patients with a higher socioeconomic status are more likely to seek medical care in larger cities, often opting for specialist facilities. Conversely, older adults who often have multiple comorbidities tend to seek consultations at local hospitals. However, due to the lack of experience with diagnosis and treatment in local hospitals, most patients were transferred to our hospital, finally reducing the impact of referral bias in our study. Additionally, our cohort indicated a higher number of females presenting with AHA, which is consistent with the CARE study [10]. The predominance of women of reproductive age also lowers the average age.

Compared with other studies, our cohort showed a higher proportion of idiopathic AHA (76.4% in our study vs approximately half in previous studies) [10,14,16]. This disparity may be partly attributed to referral bias. Patients with underlying diseases might opt to consult general hospitals, such as ours, rather than specialized centers focusing on coagulation diseases.

Our data revealed that the median duration between the onset of hemorrhagic episodes and the formal diagnosis of the total cohort was 30 days, which aligns with findings from the CARE data [10]. However, this time is longer than that in many previous studies (3-17 days) [17,18]. Notably, the median time to diagnosis for patients receiving their initial consultation at our center was 10 days. Our center is a specialized hematology facility with a relatively higher awareness of AHA and has accurate laboratory facilities for measuring FVIII levels and FVIII inhibitors titer. However, limited awareness and inadequate laboratory facilities in local hospitals may lead to delayed recognition of AHA cases in China. Therefore, it is crucial to improve clinicians' awareness of AHA and enhance laboratory capabilities in China, especially in local hospitals.

In our cohort, more than 20% of patients with AHA who experienced bleeding episodes were initially treated with FFP or CP, rather than bypassing agents, in other local hospitals to control bleeding. As expected, these patients did not achieve satisfactory outcomes. The PCC used at our center achieved a hemostatic efficacy of 80.0%. This formulation predominantly includes nonactivated prothrombin, FVII, FIX, and FX, which partially substitute deficient FVIII, thereby facilitating the restoration of clotting functionality.

In our study, the rituximab-based regimen yielded a higher CR rate (93.3%) than steroids in combination with CTX (85.0%) or steroids alone (82.4%). This finding is similar to the CARE data, which showed a higher CR rate of 90.9% in the rituximab-based regimen group compared with 87.5% in the steroids plus CTX group and 62.2% in the steroid-alone group [10]. A Spanish study also indicated that a rituximab-based regimen could achieve positive results [18].

The overall CR rate after first-line IST was 88.2%, similar to that reported in previous studies [14,17,19]. The outcomes observed in our study may exhibit a slightly more favorable trend compared with that in patients with AHA across China, as evidenced by the CARE study (81.9%) [10]. This potential improvement could be attributed to limitations in the accessibility of rituximab-based regimens for patients in the local hospitals participating in the CARE study. With the increasing use and proven efficacy of rituximab, the 2020 international AHA recommendations suggest its incorporation into first-line IST for patients with poor prognostic indicators [5]. For younger patients, the rituximab-based regimen may be a preferable choice over steroids combined with CTX due to the concerns related to the second tumor risk and reproductive toxicity associated with CTX.

Our findings indicated that FVIII inhibitor titer ≥ 15 BU/mL was a poor predictor of IST response, while the GTH-AH 01/2010 study reported that FVIII inhibitor titer ≥ 20 BU/mL was a poor predictor of IST response [20]. Additionally, we identified a BS ≥ 6 as another factor associated with poor IST response in our cohort. Previous studies also recognized FVIII activity < 1 IU/dL as an additional poor prognostic marker [14,19]. However, our study found no significant difference in CR rate or the time to CR between the patients with FVIII activity < 1 IU/dL and FVIII activity ≥ 1 IU/dL. Furthermore, patients with idiopathic AHA in our cohort exhibited a higher CR rate and lower mortality than those with associated conditions.

This study has some limitations. First, it was retrospective, and the lack of intervention randomization contributed to selection bias. Second, this single-center study had a small sample size that may have influenced our results. Third, the loss of follow-up for some patients could affect the study outcomes, especially the overall CR rate across cohorts. Patients on rituximab-based regimens exhibited better adherence to follow-up protocols in our study than those on alternative therapies (Supplementary Table S3), potentially contributing to a marginally higher CR rate across all cohorts.

In conclusion, our study reported a younger AHA population, consistent with the CARE data. Compared with earlier cohorts from

other geographic backgrounds, delayed diagnosis is a more severe issue. In patients with AHA, a rituximab-based regimen is more likely to result in CR. FVIII inhibitor titer of ≥15 BU/mL and BS of ≥6 were identified as poor predictors of CR. Further larger prospective multicenter studies are warranted to establish a more effective treatment strategy and identify additional prognostic indicators for AHA.

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ETHICS STATEMENT

This study was approved by the Human Research Ethics Committee of the Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (CIFM20210003-EC-2).

AUTHOR CONTRIBUTIONS

D.Y., R.Y., W.L., and L.Z. designed the study and wrote the manuscript. D.Y., F.X., and X.L. collected and analyzed the data. All authors read and approved the final version of the manuscript.

RELATIONSHIP DISCLOSURE

The authors have no competing interests.

DATA AVAILABILITY

The data sets used in this study are available from the corresponding authors upon reasonable request.

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SUPPLEMENTARY MATERIAL

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