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ORIGINAL ARTICLE

A single-center study of patients with rare isolated acquired clotting factor deficiencies other than acquired hemophilia A

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Abstract

Background: Isolated acquired clotting factor deficiencies (ACFDs) are mainly caused by the existence of anti-factor antibodies or adsorption of clotting factors onto substances such as amyloid. Besides acquired factor (F)VIII deficiency (acquired hemophilia A), the remaining factor deficiencies are rare and diverse, posing challenges in both diagnosis and management.

Objectives: To describe different features of isolated ACFDs to improve our understanding of these diseases and provide practical recommendations for their management.

Methods: Clinical characteristics of patients with isolated acquired FII, FV, FIX, FX, FXI, FXII, FXIII, and von Willebrand factor deficiencies were collected from a single center between July 1997 and December 2021 and analyzed retrospectively.

Results: A total of 54 rare isolated ACFD patients were enrolled in our study, mainly including 20 acquired FV deficiency patients and 16 acquired FX deficiency patients. The median age at diagnosis of all rare isolated ACFD patients was 55 years. The median time to diagnose all rare isolated ACFD patients was 60 days. Ten (18.5%) rare isolated ACFD patients had no bleeding and 2 (3.7%) rare isolated ACFD patients showed venous thromboembolism. Hemostatic treatment was applied to 41 (41/54; 75.9%) rare isolated ACFD patients. Thirty-seven (68.5%) rare isolated ACFD patients received immunosuppressive therapy, and 10 (18.5%) rare isolated ACFD patients received chemotherapy targeting primary diseases. Twenty-two (61.9%) rare isolated ACFD patients achieved complete remission, and 9 (21.4%) rare isolated ACFD patients died.

Conclusion: Rare isolated ACFDs are underestimated, associated with delayed diagnosis, and lack effective therapy. Clinicians should raise awareness for recognizing and managing rare isolated ACFD patients to avoid morbidity and mortality.

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KEYWORDS
acquired clotting factor deficiency, bleeding, diagnosis, inhibitor, immunosuppression

Essentials

- Isolated acquired clotting factor deficiencies (ACFDs) other than acquired hemophilia A are rare.
- Clinical features of 54 isolated ACFD patients at a single center were retrospectively analyzed.
- Twenty-two (61.9%) isolated ACFD patients achieved complete remission.
- Isolated ACFDs are underestimated, associated with delayed diagnosis, and lack effective therapy.

1 | INTRODUCTION

As a group of rare and heterogeneous bleeding disorders, isolated acquired clotting factor deficiencies (ACFDs) are predominantly caused by antibodies directly neutralizing or accelerating the clearance of clotting factors involving the coagulation cascade (fibrinogen, prothrombin, factor [F]V, FVII, FVIII, FIX, FX, FXI, FXII, and FXIII) and von Willebrand factor (VWF) [1]. Autoimmune diseases, malignancies, and infections are the main underlying conditions of rare isolated ACFDs [2]. The absorption of FX into deposited amyloid fibrils related to amyloidosis may cause a similar situation occasionally [3]. Rare isolated ACFDs are characterized by bleeding diathesis ranging from mild to life-threatening bleeding events, which occur spontaneously or in trauma, surgery, or invasive procedures. However, some patients still show no bleeding symptoms or even develop thrombosis [4]. Bleeding control, inhibitor elimination, and primary disease therapy are the main treatment principles for rare isolated ACFD patients to get an optimal prognosis.

The most widely spread isolated ACFD is the acquired FVIII deficiency known as acquired hemophilia A (AHA), with a reported incidence of 1.5 per million [5,6]. The remaining factors of deficiency, including FII, FV, FIX, FX, FXI, FXII, FXIII, and VWF deficiencies, are much less prevalent; even less than 20 cases of acquired FIX deficiency (AFIXD) have been reported worldwide so far [7–16]. There were lots of previous studies regarding AHA. Given the rarity, heterogeneity, and lack of specific laboratory assays in many institutions locally for rare isolated ACFDs other than AHA, it is challenging to make a timely diagnosis and implement effective management. Moreover, a comprehensive study reporting various rare isolated ACFDs together is currently lacking. We performed a retrospective study to analyze the characteristics of rare isolated ACFDs other than AHA to enhance our understanding of these diseases and provide some practical recommendations for their management.

2 | METHODS

2.1 | Patients

All patients diagnosed with rare isolated acquired FII, FV, FIX, FX, FXI, FXII, FXIII, and VWF deficiencies admitted to the Blood Disease Hospital, Chinese Academy of Medical Sciences, from July 1997 to December 2021, were consecutively enrolled through a comprehensive search within our institution's electronic medical record system. The study was approved by the Human Research Ethics Committee of the Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (CIFM20210003-EC-2).

Patients with factor activity below the normal limits (<50%; reference value, 50%-100%, which was established by our laboratory according to local conditions), or the positive clot solubility test for FXIII, and factor inhibitors titer ≥0.6 BU/mL based on Bethesda assay were included. For those patients without direct evidence of neutralizing inhibitors' existence, the diagnosis was made based on past medical history of bleeding, negative family history of hemorrhagic disease, increased clearance and decreased post-infusion recovery, and a recovery trend of coagulation factor level after immunosuppressive therapy (IST) or chemotherapy [17]. Congenital coagulation factor deficiency and factor deficiency caused by impaired synthesis or excessive consumption associated with liver disease, vitamin K deficiency, anti–vitamin K anticoagulant therapy, or disseminated intravascular coagulation were excluded.

Clinical characteristics, such as demographics, associated diseases, manifestations, laboratory tests, treatments, and outcomes were collected retrospectively. All patients were followed up from the admission to our center until March 2022. Complete remission (CR) was defined as a normal factor activity and undetectable factor inhibitors.

The bleeding severity of each patient was assessed in March 2022 retrospectively using bleeding score (BS) according to the medical history. BS is a summary score pooled by the International Society on Thrombosis and Haemostasis/Scientific and Standardization Committee Bleeding Assessment Tool (2010 version) [18]. The normal range of BS for adult males is 0 to 3, for adult females is 0 to 5, and for children is 0 to 2 [19].

2.2 | Laboratory tests

Over the past 25 years, our center has always taken identical coagulation testing. Except for FXIII, factor activity assays were performed based on the one-stage clotting assay. The patient's plasma is diluted and mixed in a

1:1 ratio with specific factor-deficient substrate plasma. Then prothrombin time (PT) or activated partial thromboplastin time (aPTT) is measured for the mixture, and the factor activity is calculated using a standard curve. The clot solubility test screened the decreased FXIII activity by observing whether the clot would dissolve within 24 hours in 5 M urea [20]. The mixing test was the initial step to screen the presence of neutralizing inhibitors. Briefly, the patient's plasma was mixed with pooled plasma from pooled normal individuals at a ratio of 1:1. Subsequently, the PT or aPTT was determined immediately and after incubation at 37 °C for 2 hours. The mixing test was considered positive when the prolonged PT or aPTT was not corrected [21]. The Bethesda method was used to measure the titer of neutralizing factor inhibitors quantitatively [22]. Pooled normal plasma was mixed 1:1 with patient plasma and incubated at 37 °C for 2 hours. Factor activity was subsequently determined and compared with the factor activity in a control plasma sample that also underwent incubation at 37 °C for 2 hours. An "inhibitor unit" was defined as the quantity capable of inactivating half of the factor activity in the patient mixture. Neutralizing FXIII inhibitors were identified by repeating the clot solubility test after mixing with normal plasma in equal quantities.

Coagulation assays were performed by a Sysmex Europe CS-5100 analyzer. The blood sample was collected into polypropylene tubes containing 0.109 mol/L sodium citrate, and then it was centrifuged at 2500 × *g* for 15 minutes to obtain blood plasma. Assays were conducted within 4 hours of collection. Samples that could not be tested immediately were stored at −20 °C (for no more than 5 days) and thawed at 37 °C immediately before assay.

2.3 | Statistical analysis

All analyses were performed using R software, version 4.1.2 (R Foundation for Statistical Computing). Comparisons between continuous variables were performed using the Mann–Whitney U-test. Comparisons between categorical variables were conducted by the chi-square test or the Kruskal–Wallis rank test. The Spearman correlation test was used to assess the correlations between variables. A *P* value of less than .05 was considered statistically significant.

3 | RESULTS

3.1 | Demographics

A total of 54 patients with rare isolated ACFD were identified, comprising 28 males and 26 females. Detailed information for all these patients is presented in Table 1. Acquired FV deficiency (AFVD) was the most commonly diagnosed rare isolated ACFD, accounting for 37.0% (20/54), followed by acquired FX deficiency (AFXD) at 29.6% (*n* = 16) and acquired FXII deficiency (AFXIID) at 9.6% (*n* = 5). Cases of other types of rare isolated ACFDs were each fewer than 5.

The median age at diagnosis for most rare isolated ACFD patients ranged from 34.5 to 62.5 years. Notably, all 4 patients with acquired FII deficiency (AFIID) were young women (<20 years old), and the sole patient with AFIXD was 13 years old. In the majority of rare isolated ACFD cases, no sex predominance was observed.

3.2 | Underlying disorders

The underlying diseases of rare isolated ACFD patients (*n* = 35; 64.8%) are detailed in Table 2. Hematologic malignancies (*n* = 18; 51.4%) were the predominantly associated condition observed in patients with AFIXD (*n* = 1; 100.0%), AFXD (*n* = 12; 75.0%), AFXIID (*n* = 4; 80.0%), and acquired von Willebrand disease (AVWD; *n* = 1; 50.0%). The only 1 AFIXD patient was secondary to leukemia. Half of the AFXD cases

TABLE 1 Characteristics of patients with isolated acquired clotting factor deficiency.

	Characteristics			
Patients[a]	Number, *n* (%)	Sex, male/female, *n*[b]	Age (y), median (range)	Days to diagnose,[c] median (range)
All	54 (100.0)	28/26	55 (4-78)	60 (2-2555)
AFIID	4 (7.4)	0/4	16 (11-19)	105 (60-1825)
AFVD	20 (37.0)	13/7	58.5 (44-71)	30 (2-1825)
AFIXD	1 (1.8)	1/0	13	60
AFXD	16 (29.6)	9/7	57 (43-78)	30 (10-730)
AFXID	4 (7.4)	2/2	34.5 (13-61)	622.5 (150-1095)
AFXIID	5 (9.6)	2/3	48 (4-53)	270 (45-2555)
AFXIIID	2 (3.7)	1/1	39, 69	180, 420
AVWD	2 (3.7)	0/2	62, 63	8, 365

AFIID, acquired factor II deficiency; AFIXD, acquired factor IX deficiency; AFVD, acquired factor V deficiency; AFXD, acquired factor X deficiency; AFXID, acquired factor XI deficiency; AFXIID, acquired factor XII deficiency; AFXIIID, acquired factor XIII deficiency; AVWD, acquired von Willebrand disease.

[a]All patients are from China with Asian ethnicity.

[b]"Sex" is used to refer to the biological differences between male and female individuals.

[c]The days to diagnose means the time from presenting bleeding diathesis or being found abnormal laboratory test to being diagnosed as isolated acquired clotting factor deficiency.

TABLE 2 Underlying diseases of patients with isolated acquired clotting factor deficiency.

	Patients, *n* (%)								
Associated conditions	**All (*N* = 54)**	**AFIID (*n* = 4)**	**AFVD (*n* = 20)**	**AFIXD (*n* = 1)**	**AFXD (*n* = 16)**	**AFXID (*n* = 4)**	**AFXIID (*n* = 5)**	**AFXIIID (*n* = 2)**	**AVWD (*n* = 2)**
None/idiopathic	**19 (35.2)**	**0 (0.0)**	**15 (75.0)**	**0 (0.0)**	**3 (18.8)**	**0 (0.0)**	**0 (0.0)**	**1 (50.0)**	**0 (0.0)**
autoimmune disease	**12 (22.2)**	**4 (100.0)**	**2 (10.0)**	**0 (0.0)**	**0 (0.0)**	**4 (100.0)**	**1 (20.0)**	**1 (50.0)**	**0 (0.0)**
SLE	4	3	0	0	0	1	0	0	0
APS	4	2	0	0	0	1	1	0	0
RA	1	0	1	0	0	0	0	0	0
SS	1	0	0	0	0	0	0	1	0
Other	2	0	1	0	0	2	0	0	0
Malignancy	**19 (35.2)**	**0 (0.0)**	**0 (0.0)**	**1 (100.0)**	**12 (75.0)**	**0 (0.0)**	**4 (80.0)**	**0 (0.0)**	**2 (100.0)**
Hematology	18	0	0	1	12	0	4	0	1
Leukemia	4	0	0	1	0	0	3	0	0
Lymphoma	1	0	0	0	0	0	1	0	0
Plasma cell dyscrasias	13	0	0	0	12	0	0	0	1
Solid tumor	1	0	0	0	0	0	0	0	1
Infectious disease	**4 (7.4)**	**0 (0.0)**	**3 (15.0)**	**0 (0.0)**	**1 (6.3)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Respiratory infection	2	0	1	0	1	0	0	0	0
Urinary tract	1	0	1	0	0	0	0	0	0
Digestive tract	1	0	1	0	0	0	0	0	0

The bold text represents the overall total for each category.

AFIID, acquired factor II deficiency; AFIXD, acquired factor IX deficiency; AFVD, acquired factor V deficiency; AFXD, acquired factor X deficiency; AFXID, acquired factor XI deficiency; AFXIID, acquired factor XII deficiency; AFXIIID, acquired factor XIII deficiency; APS, antiphospholipid syndrome; AVWD, acquired von Willebrand disease; RA, rheumatoid arthritis; SLE, systematic lupus erythematosus; SS, Sjogren syndrome.

(*n* = 8) were linked to light chain amyloidosis, and 25.0% (*n* = 4) were secondary to other plasma cell dyscrasias. Three AFXIID patients (75.0%) were associated with leukemia, while 25.0% had lymphoma. One AVWD patient (*n* = 1; 50.0%) was associated with monoclonal gammopathy of undetermined significance.

Autoimmune diseases (*n* = 12; 34.3%) were the most common underlying conditions for all AFIID patients (*n* = 4; 100%), all acquired FXI deficiency (AFXID) patients (*n* = 4; 100%), 1 acquired FXIII deficiency (AFXIIID) patients (50.0%).

While most AFVD patients (*n* = 15; 75.0%) were idiopathic, 3 AFVD patients (15.0%) were associated with infectious diseases and 2 AFVD patients (10.0%) had concurrent autoimmune diseases.

3.3 | Diagnosis

The factor activity of rare isolated ACFD patients is shown in Figure 1A. Among the 54 patients, 18 (33.3%) had extremely low factor activity (<1%), with AFVD patients constituting the majority (16/18; 88.9%).

Neutralizing factor inhibitors were identified by the Bethesda method in the majority of AFVD patients (18/20; 90.0%), 1 AFIXD patient (100.0%), 2 AFXID patients (50.0%), 2 AFXIIID patients (100.0%), and 1 AVWD patient (50.0%; Figure 1B). Nonneutralizing factor inhibitors, leading to the accelerated clearance of coagulation factors, were identified in all 4 AFIID patients (100.0%) by detecting FII activity 4 hours and 24 hours after infusion of prothrombin complex concentrate (PCC) containing nonactivated FII, FVII, FIX, and FX. The increased clearance of VWF was also observed in 1 AVWD patient (50.0%) with monoclonal gammopathy of undetermined significance after infusing plasma-derived FVIII/VWF concentrate. The exclusion of type 1C von Willebrand disease in this case was based on the significant improvement of VWF following intravenous immunoglobulin (IVIg) infusion. The presence of absorbent substances of FX was confirmed in 12 AFXD patients (75.0%) with plasma cell dyscrasias. FX inhibitors were identified in 3 AFXD patients (18.8%) by the comparison of unimproved FX activity before and after PCC infusion.

No factor inhibitors or absorbent substances were detected in 2 AFVD patients (10.0%), 1 AFXD patient (6.3%), 2 AFXID patients (50.0%), and 5 AFXIID patients (100.0%). Diagnosis in these cases relied on the absence of a hemorrhagic medical history and the significant improvement of factor levels following IST or treatment of underlying conditions.

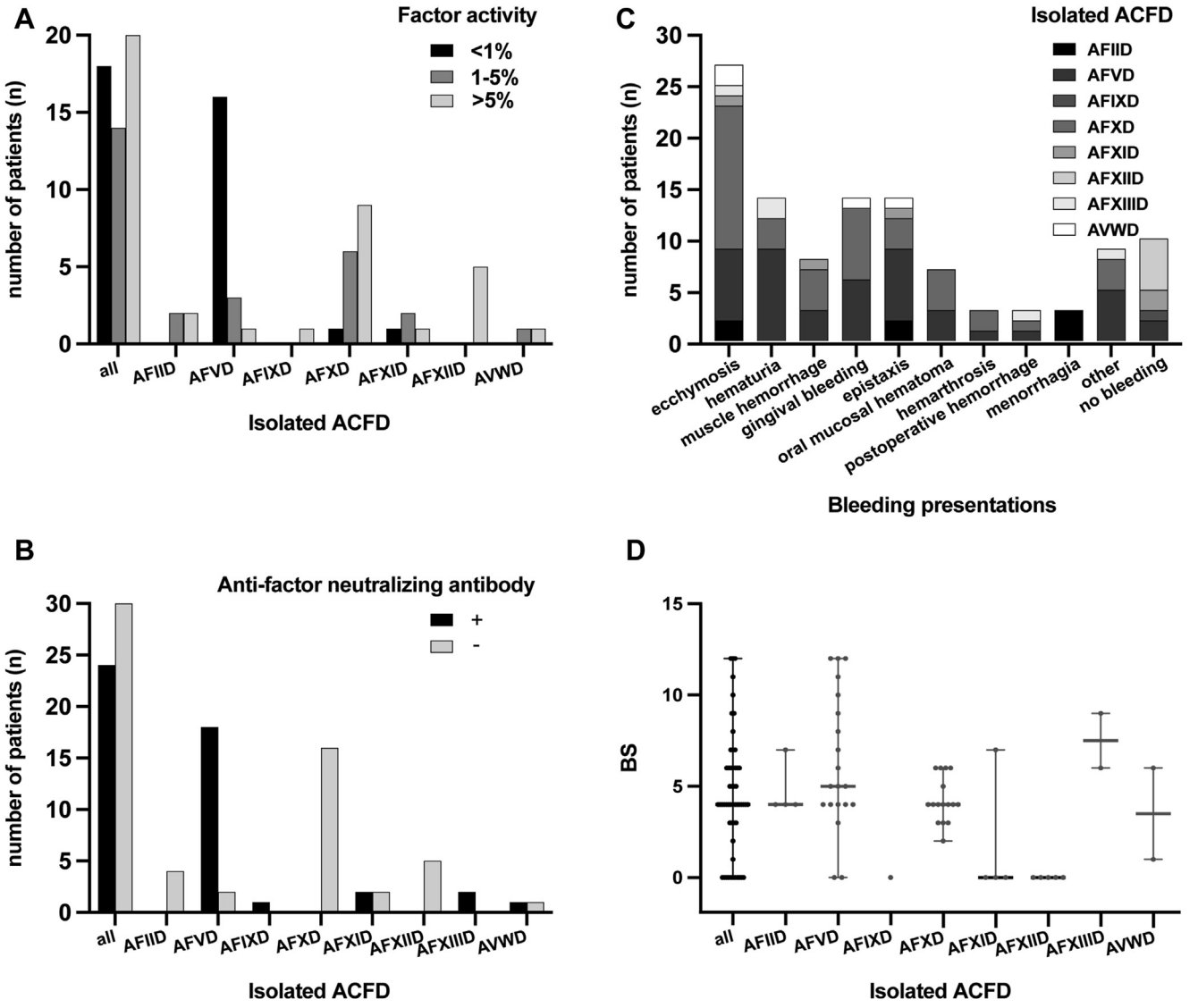

FIGURE 1 Laboratory test and bleeding presentations of patients with isolated acquired clotting factor deficiency (ACFD). (A) The number of patients with isolated ACFD who have different factor activity levels. (B) The number of patients with isolated ACFD who had been found with or without neutralizing factor inhibitors. (C) The diverse bleeding presentations of patients with isolated ACFD. (D) The bleeding score (BS) of patients with isolated ACFD. AFIID, acquired factor II deficiency; AFIXD, acquired factor IX deficiency; AFVD, acquired factor V deficiency; AFXD, acquired factor X deficiency; AFXID, acquired factor XI deficiency; AFXIID, acquired factor XII deficiency; AFXIIID, acquired factor XIII deficiency; AVWD, acquired von Willebrand disease

The initial presenting symptoms of all patients are provided in Table 3. The median time from the initial presentation of bleeding diathesis or the discovery of abnormal laboratory tests for patients to be diagnosed as AFVD and AFXD was 30 days, whereas for other rare isolated ACFD patients, it ranged from 60 to 622.5 days.

3.4 | Bleeding presentations

A total of 44 rare isolated ACFD patients (81.5%) experienced at least 1 bleeding episode at diagnosis (Figure 1C). Subcutaneous hemorrhage was the most common bleeding phenotype affecting 61.4% (27/44) of patients. Intracerebral hemorrhage occurred in 2 (2/20; 10.0%) AFVD patients and 1 (1/2; 50.0%) AFXIIID patient. Two (10.0%) AFVD patients, 1 (100.0%) AFIXD patient, 2 (50.0%) AFXID patients, and 5 (100.0%) AFXIID patients had no bleeding throughout the course of the illness. In addition, 1 (1/1; 100.0%) AFIXD patient with FIX activity of 23.6% and 1 (1/5; 20.0%) AFXIID patient with FXII activity of 27.8% showed venous thromboembolism (VTE), both of which were secondary to leukemia.

The bleeding severity varied among all rare isolated ACFD patients, showing a median BS of 4 (0-12; Figure 1D). We analyzed whether the type of factor deficiency, the factor activity, the titer of neutralizing factor inhibitors, and aPTT or PT would impact BS. Due to the extremely small sample size of some rare isolated ACFDs, analyses were simply conducted in AFVD and AFXD patients.

TABLE 3 Initial presenting symptoms of patients with isolated acquired clotting factor deficiency.

	Patients, *n* (%)								
Initial presenting symptoms	All (*N* = 54)	AFIID (*n* = 4)	AFVD (*n* = 20)	AFIXD (*n* = 1)	AFXD (*n* = 16)	AFXID (*n* = 4)	AFXIID (*n* = 5)	AFXIIID (*n* = 2)	AVWD (*n* = 2)
Bleeding	44 (81.5)	4 (100.0)	18 (90.0)	0 (0.0)	16 (100.0)	2 (50.0)	0 (0.0)	2 (100.0)	2 (100.0)
Prolonged aPTT	9 (16.7)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	2 (50.0)	5 (100.0)	0 (0.0)	0 (0.0)
Deep vein thrombosis	1 (1.9)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

AFIID, acquired factor II deficiency; AFIXD, acquired factor IX deficiency; AFVD, acquired factor V deficiency; AFXD, acquired factor X deficiency; AFXID, acquired factor XI deficiency; AFXIID, acquired factor XII deficiency; AFXIIID, acquired factor XIII deficiency; aPTT, activated partial thromboplastin time; AVWD, acquired von Willebrand disease.

No statistically significant difference in BS was observed between the AFVD patients and AFXD patients (4 vs 4; $P > .05$). Among AFVD patients, no statistically significant difference in BS was observed across mild (FV activity [FV:C], >5%), moderate (1% < FV:C ≤ 5%), and severe cases (FV:C, ≤1%; $P > .05$). Similarly, among AFXD patients, no statistically significant difference in BS was observed across mild (FX activity [FX:C], >5%), moderate (1% < FX:C ≤ 5%), and severe cases (FX:C, ≤1%; $P > .05$).

For patients with AFVD, BS was positively correlated with prolonged PT ($r = 0.71$; 95% CI, 0.38-0.87; $P < .05$) but not FV inhibitors

TABLE 4 Treatments of patients with isolated acquired clotting factor deficiency.

	Patients, *n* (%)								
Therapy	All (*N* = 54)	AFIID (*n* = 4)	AFVD (*n* = 20)	AFIXD (*n* = 1)	AFXD (*n* = 16)	AFXID (*n* = 4)	AFXIID (*n* = 5)	AFXIIID (*n* = 2)	AVWD (*n* = 2)
Hemostatic therapy	**41 (75.9)**	**4 (100.0)**	**17 (85.0)**	**0 (0.0)**	**16 (100.0)**	**1 (25.0)**	**0 (0.0)**	**2 (100.0)**	**1 (50.0)**
PCC	18	4	1	0	13	0	0	0	0
FFP	29	0	17	0	8	1	0	2	1
PLT	0	0	1	0	0	0	0	0	0
Immunosuppressive therapy	**37 (68.5)**	**4 (100.0)**	**19 (95.0)**	**0 (0.0)**	**6 (37.5)**	**4 (100.0)**	**1 (20.0)**	**2 (100.0)**	**1 (50.0)**
Steroids alone	13	3	6	0	3	1	0	0	0
Steroids + CTX	12	0	8	0	1	1	1	1	0
RTX-based	9	0	4	0	2	2	0	1	0
RTX + steroids	4	0	1	0	1	1	0	1	0
RTX + steroids + CTX	3	0	1	0	1	1	0	0	0
RTX + steroids + others	2	0	2	0	0	0	0	0	0
Others	3	1	1	0	0	0	0	0	1
Chemotherapy	**10 (18.5)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**6 (37.5)**	**0 (0.0)**	**4 (80.0)**	**0 (0.0)**	**0 (0.0)**
BCD	2	0	0	0	2	0	0	0	0
BCD + daratumumab	3	0	0	0	3	0	0	0	0
R-CHOP	1	0	0	0	1	0	0	0	0
CHOP-E	1	0	0	0	0	0	1	0	0
DA	2	0	0	0	0	0	2	0	0
VDLP	1	0	0	0	0	0	1	0	0

The bold text represents the overall total for each category.

AFIID, acquired factor II deficiency; AFIXD, acquired factor IX deficiency; AFVD, acquired factor V deficiency; AFXD, acquired factor X deficiency; AFXID, acquired factor XI deficiency; AFXIID, acquired factor XII deficiency; AFXIIID, acquired factor XIII deficiency; AVWD, acquired von Willebrand disease; BCD, bortezomib + cyclophosphamide + dexamethasone; CHOP-E, cyclophosphamide + adriamycin + vincristine + prednisone + etoposide; CTX, cyclophosphamide; DA, daunorubicin + cytarabine; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; PLT, platelets; R-CHOP; rituximab + cyclophosphamide + adriamycin + vincristine + prednisone; RTX, rituximab; VDLP, vincristine + daunorubicin + L-asparaginase + prednisone.

TABLE 5 Response to specific therapy of isolated acquired clotting factor deficiency patients.

Outcome	All (*N* = 54)	AFIID (*n* = 4)	AFVD (*n* = 20)	AFIXD (*n* = 1)	AFXD (*n* = 16)	AFXID (*n* = 4)	AFXIID (*n* = 5)	AFXIIID (*n* = 2)	AVWD (*n* = 2)
Recorded outcome, *n*	**42**	**3**	**17**	**0**	**11**	**4**	**5**	**2**	**0**
CR, *n* (%)									
Total	**26/42 (61.9)**	**3/3 (100.0)**	**13/17 (76.5)**	**0/0 (0.0)**	**2/11 (18.2)**	**2/4 (50.0)**	**5/5 (100.0)**	**1/2 (50.0)**	**0/0 (0.0)**
IST	21/32 (65.6)	3/3 (100.0)	13/17 (76.5)	0/0 (0.0)	1/5 (20.0)	2/4 (50.0)	1/1 (100.0)	1/2 (50.0)	0/0 (0.0)
Chemotherapy	5/10 (20.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	1/6 (16.7)	0/0 (0.0)	4/4 (100.0)	0/0 (0.0)	0/0 (0.0)
Dead, *n* (%)									
Total	**9/42 (21.4)**	**0/3 (0.0)**	**4/17 (23.5)**	**0/0 (0.0)**	**4/11 (36.4)**	**0/4 (0.0)**	**0/5 (0.0)**	**1/2 (50.0)**	**0/0 (0.0)**
Severe bleeding	4 (44.4)	0 (0.0)	2 (50.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)
Pulmonary infection	2 (22.2)	0 (0.0)	1 (25.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Underlying disease	1 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown reason	2 (22.2)	0 (0.0)	1 (25.0)	0 (0.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

The bold text represents the overall total for each category.

AFIID, acquired factor II deficiency; AFIXD, acquired factor IX deficiency; AFVD, acquired factor V deficiency; AFXD, acquired factor X deficiency; AFXID, acquired factor XI deficiency; AFXIID, acquired factor XII deficiency; AFXIIID, acquired factor XIII deficiency; AVWD, acquired von Willebrand disease; CR, complete remission; IST, immunosuppressive therapy.

titer (r = 0.11; 95% CI, −0.37 to 0.55; $P > .05$). For patients with AFXD, BS was directly correlated neither with aPTT (r = 0.49; 95% CI, −0.03 to 0.80; $P > .05$) nor with PT (r = 0.27; 95% CI, −0.27 to 0.68; $P > .05$).

3.5 | Hemostatic therapy

Hemostatic treatment was administered to 41 of 44 rare isolated ACFD patients (95.3%) presenting with bleeding to control or prevent secondary bleeding. The therapeutic strategies employed in our cohort are outlined in Table 4. Most rare isolated ACFD patients (n = 29; 70.7%) were given fresh frozen plasma (FFP), and most of them achieved hemostasis. One AFVD patient required a platelet transfusion, and another AFVD patient received PCC for hemostasis after an ineffective FFP treatment. One AVWD patient achieved hemostasis with IVIg after ineffective FFP. In addition, PCC was administered to all 4 AFIID patients and 13 AFXD patients to control bleeding successfully, among which 5 AFXD patients (31.3%) received FFP additionally. One AFVD patient, 1 AFXID patient, and 1 AVWD patient did not receive hemostatic agents due to mild subcutaneous bleeding.

3.6 | IST and outcome

Thirty-seven (37/54; 68.5%) rare isolated ACFD patients received IST to eradicate inhibitors, including all patients with AFIID, AFXID, and AFXIIID, the majority of AFVD patients (19/20; 95.0%), a portion of AFXD patients (6/16; 37.5%), and 1 AFXIID patient (20.0%). Steroids alone (13/37; 35.1%) and combined with cyclophosphamide (CTX; 12/37; 32.4%) were the 2 most frequent treatment regimens. Rituximab-based therapies, comprising rituximab combined with steroids, with steroids and CTX, or with steroids and other immunosuppressants, were given to 9 rare isolated ACFD patients (9/37; 24.3%).

Among 32 rare isolated ACFD patients receiving IST with recorded survival outcomes, 21 (65.6%) achieved CR, and 2 AFXID patients continued IST until follow-up. A majority of rare isolated ACFD patients achieved a high CR rate (≥50.0%), while AFXD patients exhibited an extremely low CR rate of 20.0% (Table 5).

3.7 | Primary disease-targeting therapy and outcome

Among the 8 AFXD patients diagnosed with amyloidosis, 6 (75.0%) received chemotherapy (Table 4). Subsequently, FX levels normalized in 1 patient (16.7%) who received the BCD regimen (bortezomib + CTX + dexamethasone) combined with daratumumab, while the remaining 5 continued chemotherapy until the follow-up, and the FX levels were still lower than 20% after 2 to 8 cycles of chemotherapy.

In the case of AFXIID patients, specific chemotherapy was administered to treat hematologic malignancies. FXII levels normalized in all 4 AFXIID patients (4/4; 100.0%) following chemotherapy.

3.8 | Survival outcome

Among 42 rare isolated ACFD patients who had recorded survival outcomes, 4 (4/17; 23.5%) AFVD patients, 4 (4/11; 36.4%) AFXD patients, and 1 (1/2; 50.0%) AFXIIID patient died (Table 5). Causes of death included severe bleeding (n = 4), adverse effects of IST (pulmonary infection, n = 2), underlying condition (malignancy, n = 1), and

unknown reasons (n = 2). Bleed-related deaths occurred in 2 AFVD patients, 1 AFXD patient, and 1 AFXIIID patient.

4 | DISCUSSION

This study retrospectively analyzed the clinical characteristics of rare isolated ACFDs including acquired FII, FV, FIX, FX, FXI, FXII, FXIII, and VWF deficiencies at a single center over the past 25 years, showing their rarity and heterogeneity.

Most patients with rare isolated ACFD in our cohort were in their 50s and 60s, with no apparent sex preponderance, consistent with findings reported in previous studies [7,23–26]. However, AFIID mainly affects young women, with a median age at diagnosis ranging from 13 to 22 years. This condition is often associated with lupus anticoagulant and is referred to as lupus anticoagulant with hypoprothrombinemia syndrome [27].

In our study, AFVD and AFXD were the most prevalent rare isolated ACFDs, with a median diagnosis time of 30 days [5]. Other rare isolated ACFDs were less described and showed a broader range in median time to diagnosis, spanning from 60 to 622.5 days. The underestimation and delayed recognition of these conditions may be attributed to the limited awareness among clinicians regarding these diseases and insufficient laboratory facilities for detecting such conditions in China.

Only 2 cases of AFXIIID were described in our cohort, much fewer than those reported before [26]. The FXIII activity was measured by the clot solubility test in our center, with a detection limit ranging from <0.5% to 5% FXIII activity under different test conditions [28]. This test may lack sensitivity in identifying mild or moderate FXIII deficiency, potentially resulting in the underrating of AFXIIID. In one of our AFVD patients, neutralizing inhibitors of FV with low titer were not detected until a repeated Bethesda assay was performed. The FV inhibitors in this case may not be responsive to the Bethesda assay. Furthermore, several rare isolated ACFD patients exhibited nonneutralizing factor inhibitors eluding detection by the Bethesda method. Consequently, the absence of detectable factor inhibitors via the Bethesda method does not completely rule out the diagnosis of rare isolated ACFDs. An accurate diagnosis necessitates a comprehensive medical history analysis, and more sensitive assays, such as enzyme-linked immunosorbent assay, are imperative for identifying both neutralizing and nonneutralizing antibodies [29].

In our study, not all rare isolated ACFD patients presented with bleeding episodes. Asymptomatic clinical manifestation may also lead to delayed diagnosis and underdiagnosis in these patients. Notably, our study observed thrombosis in 1 AFIXD patient and 1 AFXIID patient. It is well-established that FXII deficiency is not associated with a hemorrhagic tendency but rather plays a crucial role in inflammatory responses and thrombosis [30,31]. Therefore, for patients presenting thrombosis, rare isolated ACFDs should be considered. Conversely, elevated FIX levels are linked to an increased risk of VTE [32]. The AFIXD patient with thrombosis in our study exhibited FIX activity of 23.6% and had acute myeloid leukemia with monocytic differentiation. We postulate that the thrombosis formation might be attributed to leukemia. A previous study also reported VTE occurrence in a 27-year-old female with acute myeloid leukemia and monocytic differentiation [33].

Four bleed-related deaths (44.4%; 4/9) occurred in our cohort. The high bleed-related mortality of patients with rare isolated ACFDs observed in our study and earlier studies suggested that bleeding control is critical [23,34–36]. For patients with AVWD, severe bleeding can be addressed using bypassing agents off-label [37]. In cases where AVWD is associated with monoclonal gammopathy, IVIg proves effective in ensuring hemostasis for a duration of 3 to 5 weeks by significantly elevating VWF levels [38]. One AVWD patient in our study achieved nearly normalized VWF levels following IVIg treatment. However, there is no recommended optimal hemostatic regimen for other rare isolated ACFD patients. Coagulation factor replacement therapy is the usual but less effective therapy for rare isolated ACFDs due to the presence of antifactor antibodies or absorbent substances of factor. PCC is a substitute for AFIID, AFVIID, AFIXD, and AFXD to control bleeding. For other rare isolated ACFDs, only FFP containing a small amount of each factor is available but less effective [39]. Therefore, developing more effective hemostatic regimens for other rare isolated ACFD patients is urgently necessary. For AFVD patients, activated PCC and recombinant FVIIa are less effective since the common coagulation pathway is impaired in FV deficiency [40]. Platelet transfusion can be an effective adjunctive treatment administered with FFP, considering that platelet-derived FV may not be affected by FV inhibitors in plasma [41]. Indeed, a patient with AFVD in our study receiving platelet transfusion besides FFP administration achieved hemostasis successfully. Plasma exchange could also be used to control severe bleeding by improving factor activity and eliminating inhibiter quickly [40].

In our cohort, of those patients who were not associated with malignancies, they achieved a CR rate of more than 50% after receiving IST, except for AFXD patients, with a CR rate of 20.0%. There is no guideline specific for rare isolated ACFD patients with factor inhibitors. We largely treated them based on the IST regimen for AHA patients, such as steroids alone or combined with other immunosuppressants [42]. Only 1 AFXD patient achieved CR after receiving bortezomib-based chemotherapy during our follow-up. More effective IST needed to be found to treat AFXD patients who were not associated with plasma cell dyscrasias. The factor activity of all AFXIID patients in our study increased after receiving chemotherapy targeting the primary hematologic malignancies. Treating underlying disease also leads to the possible disappearance of acquired factor deficiencies for those patients with specific underlying etiology [43].

Overall, our study observed a poor prognosis and high mortality for many kinds of rare isolated ACFD patients, worse than AHA patients, which was reported with a CR rate of 81.9% and mortality of 6.7% in the China Acquired Hemophilia Registry study [5]. Rare isolated ACFD patients tend to be associated with hematologic malignancies, which often affect the remission of these patients. Other counts include delayed diagnosis, less effective hemostatic therapy, and lack of standard IST regimens for other rare isolated ACFD patients. Therefore, more research is needed to explore more effective treatments for rare isolated ACFD patients in the future.

This study has some limitations and biases. First, it was retrospective and some patients were lost to follow-up, which could impact the outcome of the study. Second, our study was a single-center study with a small sample size that is not that representative.

In conclusion, rare isolated ACFDs are a very heterogeneous group of disorders. Compared with AHA, other isolated ACFDs are rare, with relatively lower diagnosis rates and poorer prognoses. Therefore, clinicians should raise awareness for rare isolated ACFDs to improve the accuracy of diagnosis and explore more effective management to avoid morbidity and mortality.

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AUTHOR CONTRIBUTIONS

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

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

DATA AVAILABILITY

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

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