A Review of Coagulation Abnormalities of Autoimmune Acquired Factor V Deficiency with a Focus on Japan

Akitada Ichinose, MD, PhD[1,2] Tsukasa Osaki, PhD[1,2,3] Masayoshi Souri, PhD[1,2,3]

[1] Department of Molecular Pathobiochemistry and Pathobiology, Yamagata University School of Medicine, Yamagata, Japan
[2] The Japanese Collaborative Research Group (JCRG) on Autoimmune Acquired Coagulation Factor Deficiencies supported by the Japanese Ministry of Health, Labor and Welfare (MHLW), Yamagata, Japan
[3] Department of Public Health and Hygiene, Yamagata University Graduate School of Medical Science, Iida-Nishi, Yamagata, Japan

Address for correspondence Akitada Ichinose, MD, PhD, Department of Molecular Pathobiochemistry and Pathobiology, Yamagata University School of Medicine, Yamagata 990-9585, Japan (e-mail: aichinos@med.id.yamagata-u.ac.jp).

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Abstract

Coagulation factor V (or FV for the purpose of medical safety) is an essential cofactor of coagulation factor X in the common pathway of coagulation; severe FV deficiency leads to a bleeding tendency. Although both congenital and acquired FV deficiencies are widely recognized, FV deficiency also presents as an autoimmune disorder. A nationwide survey on autoimmune coagulation factor deficiencies (AiCFDs) conducted in Japan by our Japanese Collaborative Research Group identified 24 new patients with autoimmune FV deficiency (AiFVD) in the past 5 years. Furthermore, our extensive literature search confirmed that 177 AiFVD cases have been reported in previous articles published from Japan. Patients with AiFVD in Japan were predominantly men, with age similar to those with other AiCFDs. AiFVD was confirmed as a relatively mild type of bleeding diathesis, associated with lower mortality rate than that for AiFVD and other AiCFDs reported in previous studies. Patients with AiFVD had variable FV inhibitor titers and both neutralizing anti-FV autoantibodies and nonneutralizing counterparts. Although spontaneous resolution occurs in some patients, timely initiation of hemostatic and immunosuppressive therapies helps arrest the bleeding and eliminate anti-FV antibodies, resulting in a high cumulative recovery rate. Immunological anti-FV antibody detection is recommended to avoid missing AiFVD cases for the presence of nonneutralizing anti-FV autoantibodies. Further investigation is necessary to clarify the long-term prognosis and optimal management of AiFVD.

Keywords

- acquired coagulation factor deficiency
- autoantibody
- bleeding disorder
- factor V
- inhibitor
- nonneutralizing antibody

Coagulation factor V (or FV for the purpose of medical safety) is a cofactor of factor X (FX) in the amplification process of the clotting reaction in the coagulation cascade. Severe FV deficiency, either congenital or acquired, causes various bleeding symptoms.[1–3]

Due to increasing incidence of autoimmune coagulation factor deficiency (AiCFD) in Japan, the Japanese Collaborative Research Group (JCRG) conducted a nationwide survey on this hemorrhagic disorder during the past decade, with support of the Japanese Ministry of Health, Labor, and Welfare (MHLW).[4–6] Consequently, autoimmune deficiencies of coagulation factor XIII (or FXIII), coagulation factor VIII (or FVIII), FV, and the von Willebrand factor (VWF) have been enacted by the Japanese MHLW as the Designated Intractable Diseases (DIDs) codes 288–1, 288–2, 288–4, and 288–3, respectively. Patients with such DIDs are financially

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supported by the public medical expenses subsidy system in Japan. Autoimmune FVIII deficiency (AiFVIIID or acquired hemophilia A) is the most prevalent AiCFD, followed by autoimmune FV, FXIII, VWF, and FX deficiency (AiFVD, AiFXIIID, AiVWFD, and AiFXD, respectively); as of December 2020, the cumulative numbers of AiCFD cases in Japan are as follows: the estimated number of AiFVIIID cases is 2,160, while the reported numbers of AiFVD, AiFXIIID, AiVWD, and AiFXD cases are 173, 79, 33, and 3, respectively[4,5,7] (JCRG's achievement report 2020 to the Japanese MHLW).

According to two review articles published in 2009 and 2011, a total number of 76 and 78 patients worldwide had AiFVD, respectively[8,9] (bovine thrombin–related FV inhibitors were excluded by the authors of these articles as we did in the present study). However, these articles only included 8 and 12 AiFVD cases, respectively, described in Japan. There were no patient records of physician consultations for AiFVD at our JCRG headquarters in Yamagata University during the first 7 years (2009–2015) of our survey.

Thus, we focused our search on AiFVD cases with FV inhibitors (excluding bovine thrombin–associated cases because they are not considered autoimmune in nature) during the past 5 years (2016–2020) and identified 24 new cases through our JCRG's nationwide survey (►**Appendix A**), by employing the Governmental Diagnostic Criterion for AiFVD enacted by the Japanese MHLW (DID code: 288–4) which was analogous to 2015 Criterion for diagnosing AiFXIIID.[10] In addition, we confirmed 177 previously reported cases of AiFVD from the Japanese medical institutes through periodic extensive literature searches of English and Japanese reports in PubMed and Igaku Chuo Zasshi (ICHUSHI) databases, respectively. Herein, we aim to summarize the clinical features (abnormal laboratory findings, presenting symptoms, diagnoses, treatments, and outcomes) of 201 patients with AiFVD in Japan to improve the understanding and awareness of this disease. To the best of our knowledge, this article contains the largest number of Japan's patients with AiFVD reported so far and provides the most up-to-date overview of its patients.

Number of Autoimmune Factor V Deficiency Cases in Japan

In the past 5 years (2016–2020), more than 200 patients with suspected AiCFD participated in the JCRG survey. Among them, 24 patients were diagnosed with AiFVD due to the presence of anti-FV autoantibodies detected using immunological assays (e.g., immunoblot, immunochromatography, and enzyme-linked immunosorbent assay) and FV inhibitors detected using functional coagulation tests (e.g., Bethesda assay and FV mixing test).[11–17] Our research results do not include cases in which the bovine thrombin preparation produced an FV inhibitor due to an anti-bovine FV antibody, since the bovine thrombin preparation was no longer commercially available in Japan at that period. Based on a population size of 125 million individuals as of August 2021 (*https://www.stat.go.jp/data/jinsui/new.html*), the estimated incidence of AiFVD in Japan is at least approximately 0.04 per million persons per year.

We also conducted literature search in PubMed (last accessed on March 25, 2021) and ICHUSHI (last accessed on March 25, 2021), and identified 1,201 and 1,097 relevant reports, respectively. One suspected AiFVD case was also identified by manually searching the individual bibliographies of the identified reports.[18] By carefully perusing the results of PubMed and ICHUSHI searches, a total of 30 and 263 cases were selected as suspected AiFVD cases in Japan, respectively.

Three identified cases were excluded because of the presence of inhibitors against multiple coagulation factors and higher levels of their titers against other coagulation factors than those of titers against FV. Seven patients were excluded from our results as they had received products containing bovine thrombin–like previously reported cases[19,20] and thus, had "cross-reacting" antibodies rather than autoantibodies.[21] After excluding 98 duplicates and two cases of hereditary FVD, 201 suspected AiFVD cases were selected and classified into four subgroups according to the diagnostic criteria of the Japanese MHLW for AiFVD: "definite" ($n = 37$), "probable-2" ($n = 129$), "probable-1" ($n = 18$), and "possible" diagnoses ($n = 17$; ►**Table 1**).[22]

Since all of these AiFVD patients were reported by Japanese authors from Japanese medical institutions, they were regarded as Japanese. Based on the Japanese customs, if the patient is non-Japanese, this will be clearly stated in the article. Nevertheless, the authors used "Japan's cases" rather than "Japanese cases" in this manuscript to distinguish nationality from race when needed.

Sex Ratio

The number of male patients was higher than that of female patients, and the sex ratio (male:female) was 2.8 (►**Table 2**) which was higher than that reported in 2009 and 2011 (1.8 in 76 cases and 2.0 in 78 cases, respectively[8,9]). The difference was not significant ($p = 0.60$). The sex ratios in the AiFVIIID and AiFXIIID groups were 0.74 (52/70) and 1.21 (51/42), respectively.[23,24] The reason for the male predominance in the AiCFD group remains unknown.

Age Distribution

The mean age of patients with AiFVD was 71.9 ± 11.9 years (median, 74 years; range, 4–93 years; $n = 200$; ►**Table 2**) which was similar to that worldwide as reported in 2009 and 2011 (median, 71 years; range, 3–95 years; $n = 76$[8] and median, 69 years; range, 3–91 years; $n = 78$,[9] respectively) and in patients with AiFVIIID and AiFXIIID (median, 78 years; range, 2–98 years; $n = 154$[23] and median, 70 years; range, 22–89 years; $n = 93$,[24] respectively). The mean age was apparently higher in patients with AiFVD than in those with AiFXD (56.5 years, $n = 26$[7]) as AiFVD occurred in only one patient aged <30 years. Although the age of the non-bleeder group tended to be slightly higher than that of the bleeder group (►**Fig. 1A**), the difference was not significant ($p = 0.27$). Old age per se is not a criterion to suspect AiFVD because some patients have been diagnosed with congenital FVD at the ages of 80 and 88 years.[25,26]

Table 1 Governmental Diagnostic Criterion for AiFVD enacted by the Japanese Ministry of Health, Labor, and Welfare (the Designated Intractable Disease code: 288–4)

Patients with "definite" or "probable" diagnosis will be provided with governmental medial/financial support
A. Symptoms and others
1. Recent onset of bleeding symptoms (developed within the previous year mainly in older adults)
2. No family history of congenital/inherited deficiency of FV/5 (nor other coagulation factor deficiencies)
3. Lack of previous bleeding symptoms especially in association with previous hemostatic challenges (e.g., trauma, surgery, invasive tests, tooth extraction, and delivery)
4. Bleeding symptoms are not due to the excessive use of certain medications such as anticoagulants and antiplatelet drugs
B. Laboratory findings
1. Abnormality of FV parameter(s) on specific laboratory testing (usually FV activity and/or antigen <50% of reference levels)
(1) FV activity (FV:C): always extremely low
(2) FV antigen (FV:Ag): usually variably low
(3) FV specific activity (FV:C/FV:Ag ratio): usually variably low
2. Laboratory tests for definite diagnosis
(1) PT and/or aPTT cross-mixing test showed an inhibitor pattern in the presence of isolated severe FV deficiency
(2) The FV inhibitor (circulating anticoagulant) is positive
Results of the 1:1 mixing test of FV activity between patient's plasma and normal control's plasma (50% each) was not corrected
Measurement of inhibitor titer: The residual FV activity of mixed plasma between patient's diluted plasma and healthy control's plasma was measured after incubation at 37°C for 2 hours (Bethesda method)
(3) Detection of anti-FV autoantibodies
Noninhibitory antibodies can be detected by binding methods (immunoblot, enzyme-linked immunosorbent assay, immunochromatography, etc.). FV inhibitors, that is, neutralizing anti-FV autoantibodies, are also detected using immunological methods
C. Differential diagnosis
Parahemophilia (hereditary FV deficiency), congenital combined FV and factor VIII/8 deficiency, all secondary FV deficiencies (including disseminated intravascular coagulation, severe liver disorder, etc.), inherited factor X/10 (FX) deficiency, autoimmune FX deficiency, all secondary FX deficiencies, inherited prothrombin deficiency, autoimmune prothrombin deficiency, all secondary prothrombin deficiencies, autoimmune acquired factor XIII/13 deficiency, anti-phospholipid antibody syndrome, etc., were excluded
Diagnosis category
Definite: All A items plus B1 and B2-(3), but all C items must be excluded
Probable: All A items plus B1 plus B2-(1) or B2-(2), but all C items must be excluded
Probable-1: All A items plus B1 plus B2-(1), but all C items must be excluded
Probable-2: All A items plus B1 plus B2-(2), but all C items must be excluded
Possible: All of A items plus B1

Abbreviations: Ag, antigen; AiFVD, autoimmune factor V deficiency; aPTT, activated partial thromboplastin time; FV, factor V; PT, prothrombin time.

Underlying Diseases/Conditions

Fifty-eight patients (28.9%) with AiFVD had no underlying conditions (that is idiopathic origin; ►**Table 3**; ►**Fig. 1B**). Meanwhile, 39 (19.4%) patients with AiFVD had infectious diseases (mainly involving the respiratory system), and 34 (16.9%) patients were administered antibiotics which may be related to development of anti-FV autoantibodies, as previously reported in patients who had anti-FXIII autoantibodies.[24] Thirty-four patients (16.9%) underwent surgery. The causality or association in these cases is difficult to prove because their implicated conditions are commonly encountered in the normal population,[8,9] and surgery, infection, and antibiotic therapy frequently occur sequentially and/or simultaneously in patients with AiFVD. However, a relationship between the drug used and development of FV inhibitors was established in a few cases; in one patient, FV inhibitors disappeared 3 weeks after treatment with dabigatran was discontinued, but reappeared after the medication was readministered.[27] The presence and disappearance of immunoglobulin (Ig)-G-type anti-FV autoantibodies was confirmed in this patient by enzyme-linked immunosorbent assay (paper in preparation). Similar incidents have been reported in two other patients treated with aspirin and antibiotics.[28,29]

Table 2 Sex and age information

	Subgroup	Total	F	M	n.d.	M/F rate	Male (%)	*p*-Value
Sex	Total	201	52	146	3	2.81	73.7	
	Bleeder	138	33	102	3	3.09	73.9	0.60
	Nonbleeder	59	17	42	0	2.47	71.2	
	Subgroup	**Total**	**Average**	**SD**	**Maximum**	**Minimum**	**Median**	***p*-Value**
Age	Total	200	71.9	11.9	93	4	74	
	Bleeder	137	71.5	11.1	93	36	73	0.27
	Nonbleeder	59	72.6	13.5	92	4	75	

Abbreviations: F, female; M, male; n.d., not described; SD, standard deviation.

Twenty-three (11.4%) Japan's patients with AiFVD had autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. Fifteen (7.5%) patients developed AiFVD during hemodialysis which was detected due to persistent bleeding from puncture sites, and/or abnormal findings in repeated routine coagulation tests.

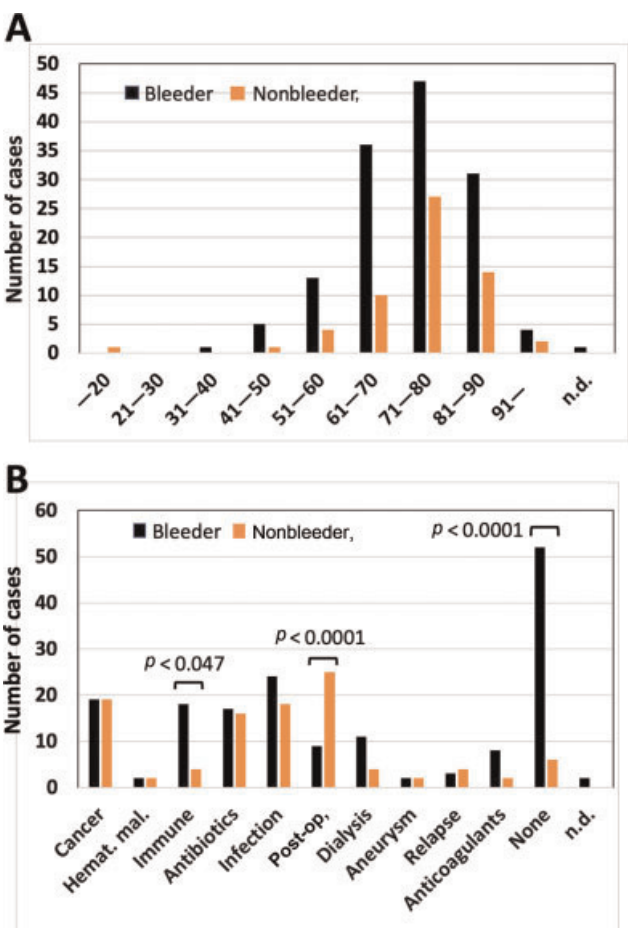

Fig. 1 Patients' characteristics. (**A**) Age distribution. AiFVD was frequently detected in individuals >60 years of age. The second peak age of bleeders was younger than that of nonbleeders. (**B**) Underlying diseases and conditions. More than one-fourth of AiFVD cases are idiopathic, and approximately one-fifth are associated with infection. AiFVD, autoimmune factor V deficiency; Hemat. mal., hematopoietic malignancies; n.d., not described; Post-op, postoperative.

Notably, solid cancers ($n = 39$; 19.4%) and hematopoietic malignancies ($n = 4$; 2.0%) were found in patients with AiFVD. The destruction of malignant cells may contribute to the dysregulation of the inflammatory immune response.

Significant differences were found in the frequencies of surgery-associated and idiopathic cases (both $p < 0.0001$) between bleeders and nonbleeders (6.5 vs. 43.1 and 37.7 vs. 8.6%, respectively). Therefore, bleeders were more likely to have an idiopathic origin, whereas nonbleeders were more likely to be related to surgery.

Bleeding Sites/Symptoms and Bleeding Severity

AiFVD symptoms vary from no hemorrhage to life-threatening bleedings and thrombotic complications.[8,9,21] Fifty-nine (29.4%) patients had no bleeding symptoms (►**Fig. 2A**), although patients may manifested bleeding events after 6 years of close monitoring.[30] Most patients with AiFVD demonstrated bleeding in soft-tissue regions, such as subcutaneous tissues (26.4%), urinary tract (23.4%), and intestine (19.4%). Intracranial (6.5%) and intraperitoneal (4%) bleeding events were reported in AiFVD patients, similar to those with AiFVIIID and AiFXIIID.[23,24] The AiFVD patients in Japan reported bleeding in the subcutaneous tissues more frequently than those in all countries worldwide[8,9] (26.4 vs. 9.2%, $p = 0.0001$). It is possible that Japanese patients and their attending physicians might have focused more attention to bleeding symptoms, resulting in this difference in frequency. Postoperation bleeding, post-tooth extraction, and post–needle puncture are not specific to AiFVD but are common among patients in Japan and all countries worldwide (5.9–11%[8,9]).

According to the published categories of clinical bleeding severity,[31] 41.3% of patients with AiFVD had grade-III bleeding (►**Fig. 2B**), indicating that this disease may be more severe than congenital FVD[1,2] in which only 14% of patients experienced grade-III bleeding.[31]

Nine (4.5%) AiFVD patients in Japan developed thrombosis as a complication.[11,16,18,32–38] FV autoantibodies may inhibit the anticoagulant properties of FV,[21,39] including its function as an activated protein C cofactor in inactivation of activated factor VIII[40,41] and activated factor V.[42]

Table 3 Underlying diseases/conditions

	Bleeder	Percentage	Nonbleeder	Percentage	*p*-Value
Cancer	19	13.8	19	32.8	0.10
Hemot. mal.	2	1.4	2	3.4	0.62
Immune	18	13.0	4	6.9	**0.0465**
Antibiotics	17	12.3	16	27.6	0.18
Infection	24	17.4	18	31.0	0.47
Post-op	9	6.5	25	43.1	**<0.0001**
Dialysis	11	8.0	4	6.9	0.36
Aneurysm	2	1.4	2	3.4	0.31
Relapse	3	2.2	4	6.9	0.29
Anticoagulants	8	5.8	2	3.4	0.23
None	52	37.7	6	8.6	**<0.0001**
n.d.	2	1.4	0	0.0	0.27

Abbreviations: Hemat. mal., hematopoietic malignancies; Immune, autoimmune disease; Post-op, postoperation;
Note: Bold *p*-values indicate statistical significance.

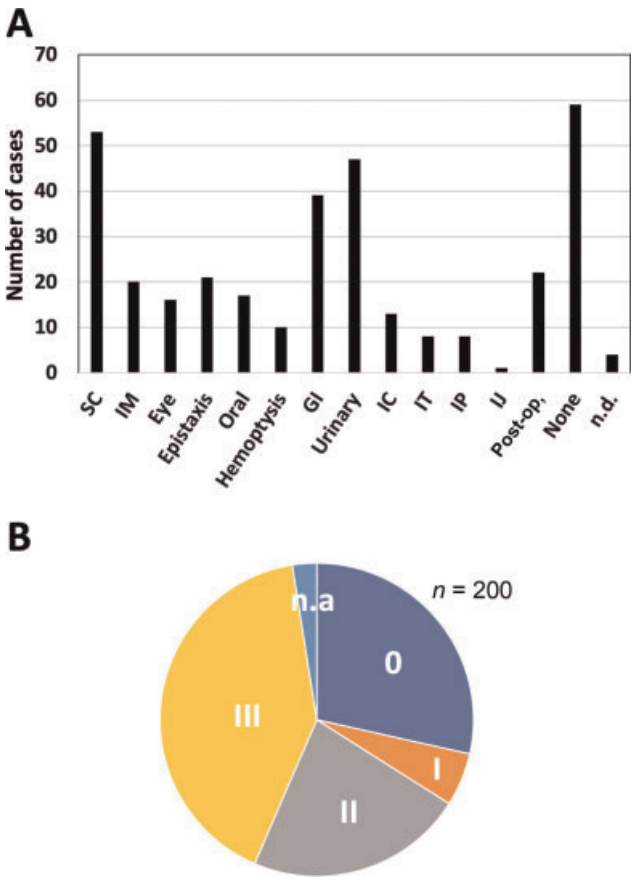

Fig. 2 Bleeding symptoms. (**A**) Bleeding sites. Fifty-nine AiFVD patients did not present with bleeding events. Conversely, many patients had more than one bleeding site and/or symptom. In total, 138 AiFVD patients experienced 275 bleeding events (2.0 on average). (**B**) Severity of clinical bleeding. Ratio of bleeding grades. n.a. represents not applicable because bleeding sites/symptoms were not described. AiFVD, autoimmune factor V deficiency; GI, gastrointestinal; Post, postoperative; IC, intracranial; IJ, intrajoint; IM, intramuscular; IT, intrathoracic; IP, intraperitoneal; IJ, intrajoint; n.d., not described; Post-op, postoperative; SC, subcutaneous.

Abnormal Results on Routine Tests

The mean hemoglobin level in patients with AiFVD was 108 ± 67 g/L (median, 96 g/L; $n = 25$) which is consistent with the fact that two-thirds (138/200) of AiFVD patients presented with bleeding symptoms (►**Fig. 2B**). The mean hemoglobin level in the bleeder group was significantly lower than that in the nonbleeder group (91.7 ± 31.1 vs. 159 ± 117 g/L, $p < 0.042$; ►**Table 4** top) and was significantly related with the bleeding severity ($p < 0.02$; ►**Fig. 3A**). The mean platelet count was normal ($233 \pm 122 \times 10^9$/L, $n = 91$; ►**Table 4** top).

Concomitant Prolongation of Prothrombin Time and Activated Partial Thromboplastin Time and Decrease in Factor V Activity (FV:C)

Both prothrombin time (PT) and activated partial thromboplastin time (aPTT) were considerably prolonged in AiFVD patients, indicating abnormalities in factors in the common pathway of the coagulation cascade. Japan's AiFVD bleeders had statistically longer PT and aPTT than Japan's nonbleeders (63 vs. 43.2 seconds $p < 0.004$ and 156.1 vs. 126.8 seconds $p < 0.005$, respectively; ►**Table 4** middle). PT and aPTT were significantly correlated ($p < 0.0001$; ►**Fig. 3D**). As expected, both PT and aPTT were significantly correlated with bleeding severity ($p \leq 0.0042$ and 0.0029, respectively; ►**Fig. 3B** and **C**). Patients with markedly prolonged PT and aPTT should be monitored closely, as highlighted in a previous review.[8] The hepaplastin test (HPT) was performed in 35 AiFVD patients, and the results were normal ($97 \pm 26.8\%$; ►**Table 4** bottom); this is consistent with findings from our previous study, that HPT can differentiate FV deficiency from other coagulation factor deficiencies.[43]

FV:C was severely reduced in AiFVD bleeders ($2.9 \pm 2.9\%$, $n = 173$; ►**Table 4** top) which may be associated with a relatively severe bleeding tendency. However, no clear

Table 4 Results of laboratory tests

	Subgroup	Total	Average	SD	Maximum	Minimum	Median	*p*-Value
Hemoglobin (g/L)	Bleeder	19	91.7	31.1	171	51	82	**0.0417**
	Nonbleeder	6	159	117	398	101	116	
Platelet ($\times 10^9$/L)	Bleeder	67	228	119	694	1	244	0.61
	Nonbleeder	23	251	135	520	70	206	
FV:C (%)	Bleeder	116	2.9	2.6	14	0	3.0	0.87
	Nonbleeder	50	3.0	3.7	26	0	3.0	
FV:Ag (%)	Bleeder	5	17.0	9.5	29	7	14.3	*0.05*
	Nonbleeder	2	55.6	34.8	80.2	31	55.6	
PT(s)	Bleeder	60	63.0	42.8	301	17.5	57.8	**0.0037**
	Nonbleeder	31	43.2	17.7	104.9	19.2	38.9	
PT (INR)	Bleeder	43	7.4	3.7	20.5	2.34	6.8	**0.0005**
	Nonbleeder	40	4.9	2.0	11.8	2.18	4.6	
PT (%)	Bleeder	40	12.8	14.8	86.1	2	9	**0.0152**
	Nonbleeder	15	12.6	2.8	20	10	12	
aPTT(s)	Bleeder	98	156.1	61.2	331	35	154.1	**0.0045**
	Nonbleeder	54	126.8	51.0	265.1	46.8	132.1	
Lupus anticoagulant[a]	Bleeder	12	1.35	0.26	1.79	0.9	1.36	**0.0349**
	Nonbleeder	10	1.2	0.1	1.45	1.03	1.2	
FV Inhibitor (BU/mL)	Bleeder	90	46.0	170.6	1500	0.69	4.95	0.17
	Nonbleeder	35	48.8	165.9	969	1	8	
Inhibitory pot. (%)[b]	Bleeder	3	29.0	12.3	41	16.5	29.5	0.65
	Nonbleeder	1	–	28	28	28	28	
Hepaplastin test (%)	Bleeder	23	99.4	29.0	166	36.9	96.2	0.44
	Nonbleeder	12	92.3	22.5	130	49	89.5	
Day to recovery	Bleeder	76	33.1	45.6	365	4	20	0.07
	Nonbleeder	36	58.3	76.0	360	5	29	

Abbreviations: Ag, antigen; aPTT, activated partial thromboplastin time; FV, factor V; Inhibitory pot.; inhibitory potential; INR, international normalized ratio; PT, prothrombin time; SD, standard deviation.
Note: Bold *p*-values indicate statistical significance.
[a]Numbers indicate ratio of diluted Russell viper venom times for screen (low phospholipid) and confirm (high phospholipid) assays.
[b]Calculated as described in the ►**Appendix A** section.[66]

correlation was found between FV:C levels and bleeding severity ($p = 0.66$); the correlation between the FV level and bleeding phenotype was previously reported to be lost or limited in the group with low FV range (<5%), wherein patients with equal FV levels may demonstrate different clinical phenotypes.[1] In contrast to the reports of a previous study,[8] no significant difference was observed in FV:C between the bleeder and nonbleeder groups (2.9 vs. 3%, $p = 0.87$) in this study. This was likely because the Japanese commercial laboratories uniformly report extremely prolonged one-stage clotting time assays for FV activity as "< 3%." Naturally, the FV:C levels were significantly correlated with both PT and aPTT ($p = 0.007$ and <0.0001, respectively; ►**Fig. 3E** and **F**).

Although the number of tested samples was limited, the FV:antigen (Ag) level varied from normal to extremely low in patients with AiFVD (28.0 ± 24.8%, $n = 7$). Thus, the specific activity of FV (FV:C/FV:Ag) was low (0.03 and 0.09 in two patients[44,45]). This finding is consistent with the idea that at least some FV molecules are inhibited by neutralizing anti-FV antibodies (i.e., FV inhibitor), resulting in the formation of an antigen–antibody complex and a reduction in the specific activity of FV.

Mixing tests based on PT and/or aPTT were performed in 130 patients, 111 showing an inhibitor pattern, while 19 demonstrated a deficiency pattern (data not shown). A deficiency pattern can change to an inhibitor pattern in the same patient, as reported in at least four patients with AiFXIIID.[46–48] This is likely because when an inhibitor potency is low, the FV inhibitor is overwhelmed by FV in normal plasma used for the mixing test assay. Conversely, when an inhibitor potency increases, the FV in normal plasma is overwhelmed by patient's inhibitor. Accordingly, physicians should either examine the FV inhibitor titer and/or repeat mixing tests when acquired FVD persists for a prolonged period.

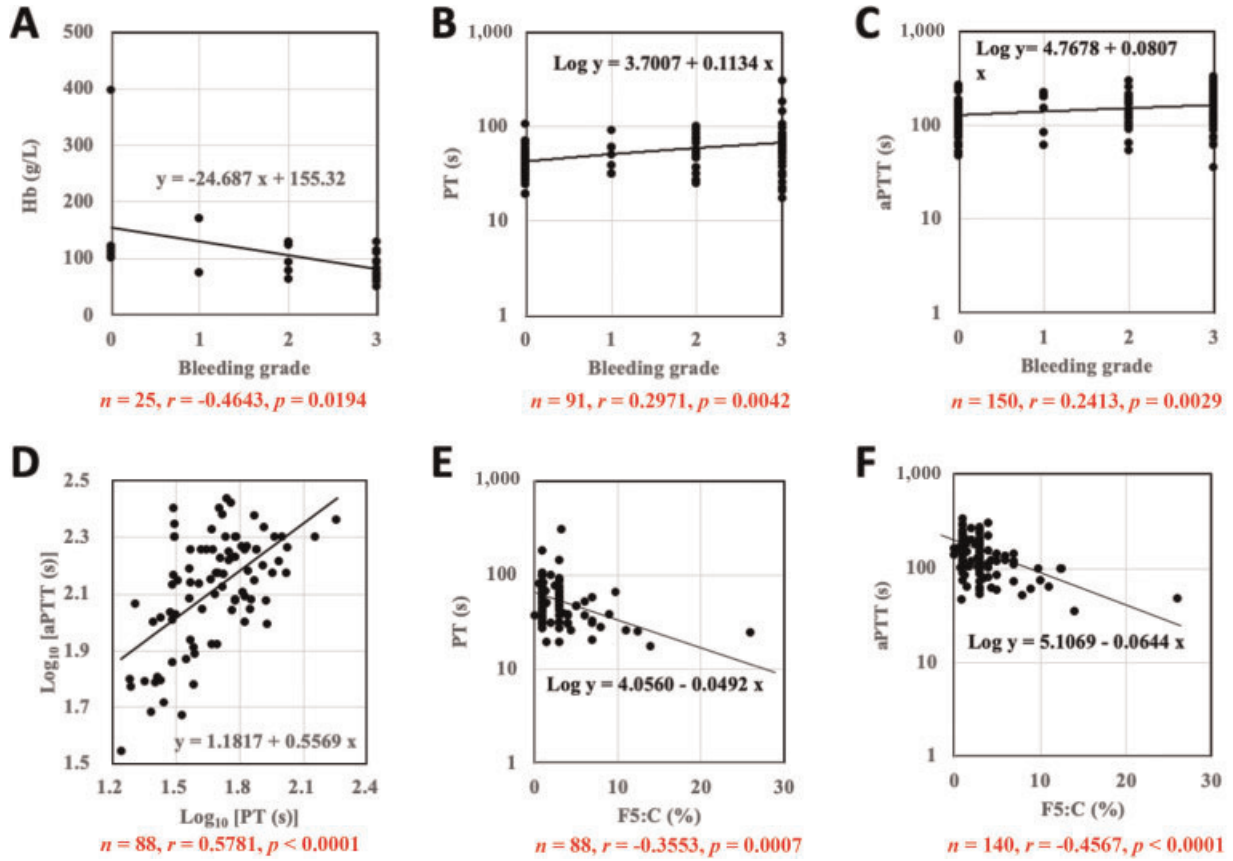

Fig. 3 Correlation between parameters. (**A**) Relationship between bleeding severity and hemoglobin (Hb) levels. (**B**) Relationship between bleeding severity and prothrombin time (PT) (s). (**C**) Relationship between bleeding severity and activated partial thromboplastin time (aPTT)

The FV inhibitor titer was determined in 127 AiFVD patients and varied widely (46.3 ± 167.3 BU/mL; ►**Table 4** middle). Two patients showed a titer lower than the cut-off value (<0.5 BU/mL) despite having anti-FV autoantibodies, suggesting the presence of nonneutralizing autoantibodies and/or FV-antigen-antibody complex[16] (unpublished data). Unexpectedly, FV inhibitor titer was not correlated with bleeding severity, hemoglobin level, PT, aPTT, and FV:C levels ($p = 0.88$, 0.65, 0.72, 0.61, and 0.64, respectively; data not shown).

The lupus anticoagulant (LA) test was conducted in 48/201 patients with AiFVD, and results showed that LAs were positive (= abnormal if >1.3), negative, and unmeasurable in 11, 28, and 9 patients, respectively (data not shown). Anticardiolipin and anti-β_2-glycoprotein antibodies were positive in 6 and 2 patients but negative in 30 and 38 patients, respectively (data not shown). Both LA and anticardiolipin (or anti-β_2-glycoprotein antibody) were positive in four patients which demonstrated isolated FV deficiency.[49–52] Their FV inhibitors disappeared shortly after initiation of steroid pulse therapy, administration of prednisolone, and absence of immunosuppressive therapy, respectively. Thus, the expression of FV inhibitor in these cases was unlikely caused by presence of an antiphospholipid antibody which is usually resistant to immunosuppressive therapies.

Anti-Factor V Autoantibodies

Anti-FV autoantibodies could only be detected in 37 patients with AiFVD (data not shown), mainly because anti-FV autoantibody detection tests are not routinely performed in Japan. Among these patients, 34 had IgG class and two had IgA class anti-FV autoantibodies. One patient had anti-FV autoantibodies, although the sample did not show a positive result for FV inhibitor,[16] suggesting the presence of nonneutralizing autoantibodies against FV and/or FV-antigen-antibody complexes, as reported by Cortier et al.[53] Similarly, another patient showed low FV:C level (5%) in absence of an FV inhibitor and negative mixing test (paper in preparation). All patients with suspected AiFVD should be immunologically tested for anti-FV autoantibodies since functional FV inhibitor assays are unable to detect nonneutralizing autoantibodies against FV.

Therefore, some patients with suspected AiFVD have nonneutralizing autoantibodies against FV when they display extremely low FV:C levels in the absence of an FV inhibitor and/or negative mixing test.

Hemostatic Treatment

A total of 110 (54.7%) patients with AiFVD received hemostatic therapy, while 29 (14.4%) patients did not receive (►**Fig. 4A**). Fresh frozen plasma (FFP) was administered in

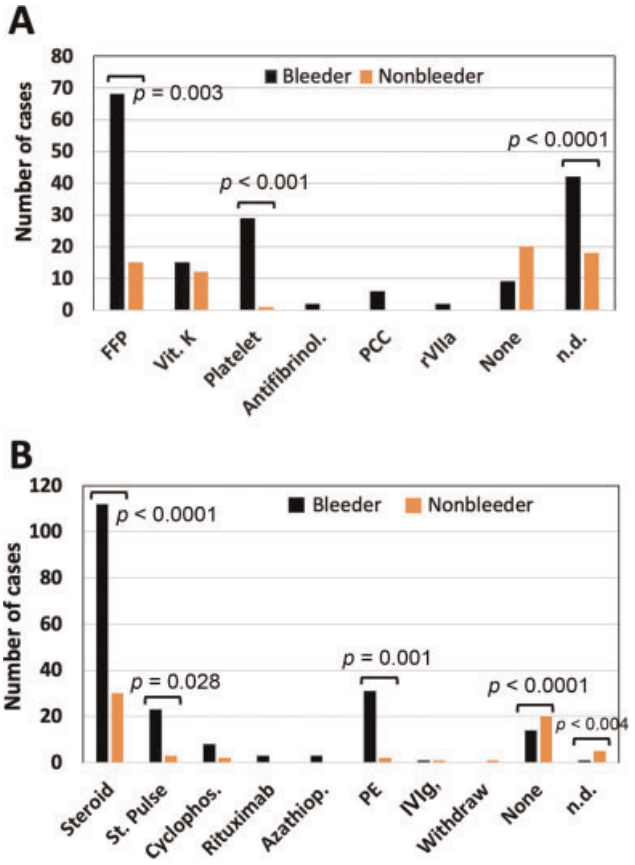

Fig. 4 Treatment. (**A**) Hemostatic therapy. Fresh frozen plasma (FFP) was most frequently administered to AiFVD patients, followed by platelet concentrates (platelet). (**B**) Antibody-eradication/reduction therapy. Prednisolone ("Steroid") was most frequently used in both bleeders and nonbleeders in high doses or pulse administration. Bleeders often undergo plasma exchange (PE) and rarely receive high-dose intravenous immunoglobulin (IVIg) treatment. These regimens were employed much less frequently in nonbleeders. AiFVD, autoimmune factor V deficiency; antifibrinol., antifibrinolytics; Azathiop., azathioprine; Cyclophos., cyclophosphamide; n.d., not described; PCC, prothrombin complex concentrates; rVIIa, activated recombinant factor VII; Withdraw, withdrawal; Vit. K, vitamin K.

42.3% of patients with AiFVD but was ineffective in arresting bleeding (success rates: 11.8 and 15.4% in Japan and worldwide, respectively; ►**Table 5** top). This is likely because FFP contains only 1 U/mL of FV and is easily overwhelmed by FV neutralizing autoantibodies. The repeat administration of FFP may be risky in patients with ongoing bleeding because of possible circulatory overload,[54] aggravation of bleeding symptoms,[55] and coagulation abnormalities such as an increase in FV inhibitor titer.

To date, there are no available commercial FV concentrates. As an alternative, platelet concentrates were used in 14.9% of patients as platelets contain 20% plasma FV.[56] The success rates were 26.7% (8/30) and 68.8% (11/16) in Japan and worldwide, respectively. The dose and frequency of platelet transfusion may differ from patient to patient and country to country; thus, its hemostatic effect may also differ between Japan and the rest of the world. Vitamin K was administered in 13.9% of patients in Japan, but it had no effect on bleeding, confirming that vitamin-K deficiency was not the cause of bleeding in patients with AiFVD.

Table 5 Efficacy of therapy

	Cases	Cases showing efficacy
	Administered	Number (%)
Hemostatic treatment		
FFP	85	10 (11.8)
Vitamin K	28	0 (0)
Platelet	30	8 (26.7)
Antifibrinolytics	2	0 (0)
PCC	7	2 (28.6)
rVIIa	2	1 (50)
Antibody eradication/ reduction therapy		
Steroid alone	101	86 (85.1)
St. pulse alone	10	9 (90)
Combined[a]	9	9 (100)
Cyclophosphamide	4	3 (75)
Combined[a]	6	3 (50)
Plasma exchange	10	6 (60)
Combined[a]	9	5 (55.6)

Abbreviations: FFP, fresh frozen plasma; PCC, prothrombin complex concentrates; rVIIa, recombinant activated factor VII; St., steroid.
[a]Employed in association with other immunosuppressants; steroid, mostly prednisolone.

Prothrombin complex concentrates (PCCs) and recombinant-activated factor VII (rFVIIa) were used in 3.5 and 1% patients with AiFVD, respectively. Antifibrinolytic agents, such as tranexamic acid, were used in only 1% of patients with AiFVD; this may be because the patients did not present a hyperfibrinolytic state. Although variable success rates of PCCs have been reported in Japan and worldwide (28.6 and 80%, respectively), the number of patients (seven and five cases, respectively) was relatively small to draw any meaningful conclusion.

Hemostatic medicine was not administered in 14.4% of Japan's AiFVD patients or was not described (ND) in 30.8% of patients, mainly because these patients did not show any bleeding symptoms or their bleeding symptoms were not severe.

Antibody Eradication/Reduction Therapy

In total, 73% of Japanese patients with AiFVD initially received prednisolone with or without other associated treatments (overall prednisolone) for antibody eradication (►**Fig. 4B**), while 13.5% patients received a pulse prednisolone regimen, with success rates of 74.7 and 70.8%, respectively (►**Table 5**, bottom). The success rate of prednisolone alone was higher (85.4%) than that of the overall prednisolone. Moreover, pulse prednisolone alone had 90% success rate, while pulse prednisolone combined with prednisolone

had 100% success rate (►**Table 5**, bottom). Therefore, physicians should select either the pulse prednisolone alone regimen or the combined regimen as a first-line antibody eradication therapy whenever possible.

Cyclophosphamide and rituximab, an anti-CD20 monoclonal antibody, were used only in 5.1 and 1.5% of patients with AiFVD, respectively, possibly because they are not approved for treatment of AiFVDs by the Japanese public health insurance system.

Plasma exchange (PE) and high-dose intravenous immunoglobulin (IVIg) therapy were administered to 17 and 1% of patients with AiFVD in Japan, respectively. Although PE showed a success rate of 60% in reducing the level of antibodies, the effect of PE is theoretically transient in nature, as indicated by the temporary success rate of 50%. None of the Japan's patients with AiFVD underwent antibody adsorption therapy. Moreover, IVIg was rarely used in AiFVD patients, as reported in AiFXIIID patients. [24] Furthermore, IVIg is not recommended by the Japanese Society of Thrombosis and Hemostasis for management of AiFVIIID[57] due to the variable effects of this treatment.[23]

Antibody-directed therapy was not performed in 17.2% of Japan's patients with AiFVD, while it was not performed in 5 and 11.8% of patients with AiFVD and AiFXIIID, respectively[23,24]). It is likely that some patients with AiFVD did not need this treatment or that their acquired FVD was transient and self-limiting.

Prognosis

Outcomes were reported in 192 (95.5%) patients with AiFVD (►**Fig. 5A**); of the 147 (73.5%) patients who achieved resolution, 21 (10.5%) showed spontaneous resolution. Similar overall and spontaneous resolution rates were previously reported in 69.2% (54/78) and 15.4% (12/54) of patients with FV inhibitor, respectively.[9] A total of 10 (5%) patients showed disease deterioration after reinitiating the antibiotic therapy,[29] administering FFP infusion,[55] or tapering the dose of prednisolone.[49,54,58,59]

With regard to the all-cause mortality among the 201 patients with AiFVD, 30 (15% of 201 cases) patients died (►**Fig. 5B**); this mortality rate (15%) was 50% lower than that reported in a previous worldwide review article (23/75, 30.7%[8]). In addition, 13 (6.5% of 201 cases) Japan's AiFVD patients died due to hemorrhagic complications such as brain hemorrhage, peritoneal hemorrhage, hemorrhagic shock due to systemic bleedings or gastric bleeding, etc.; this mortality rate (6.5%) was approximately 50% lower than that reported in a previous worldwide review article (9/75, 12%[8]). The major differences between the present and the previous review articles are as follows: sample size: 201 cases versus 75 cases[8]; study population: single country versus worldwide[8]; and study period: April 2011 to March 2021 versus 1950 to June 2008.[8] A total of 69 Japanese patients were diagnosed with AiFVD before 2010, while 132 patients were diagnosed with AiFVD after 2011. Because the numbers of both reported and recovered AiFVD cases have approximately two-fold increase over the past 10 years,

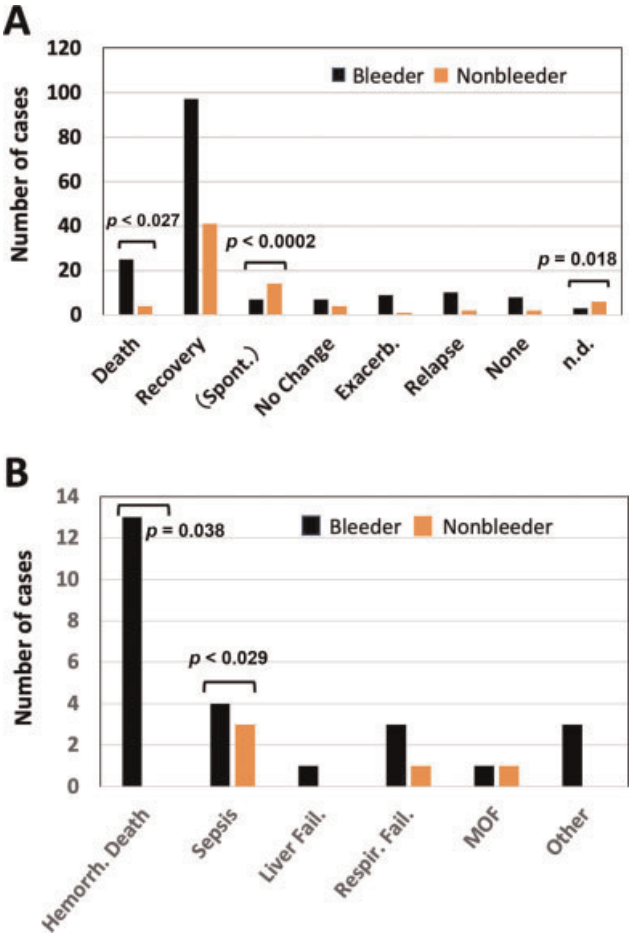

Fig. 5 Prognosis. (A) Outcome of AiFVD. The majority of patients recovered regardless of whether they are categorized as bleeders or nonbleeders. Spontaneous (Spont.) recovery occurred more frequently in nonbleeders than in bleeders ($p < 0.0002$), while all-cause death was more frequent in bleeders than in non-bleeders ($p = 0.027$). (B) Causes of death. Hemorrhagic (Hemorrh.) death occurred only in bleeders, while septic death occurred more frequently in non-bleeders. AiFVD, autoimmune factor V deficiency; Exacerb., exacerbation; Fail., failure; MOF, multiple organ failure; n.d., not described.

there may have been a significant progress in the awareness and management of this disease, that is, prompt diagnosis was performed and appropriate treatment was provided. However, the exact reason why Japanese patients with AiFVD have more favorable outcome remains unclear.

The rate of hemorrhagic death (6.5%) was not higher in the AiFVD patients than in the AiFVIIID and AiFXIIID patients (9.1% [13/143] vs. 14% [13/93][23,24]).

Relapse was reported in 11.4% (22/201) of AiFVD patients. Two patients experienced relapse 4 years after remission.[12,60] Thus, long-term observation of patients with AiFVD is necessary. In particular, relapse tends to occur when patients undergo surgery and/or receive antibiotic therapy.[12,60]

The median time and range to recovery were 25 days and 4 to 365 (40.8 ± 57.6) days in Japan's AiFVD patients, respectively (►**Table 4** bottom). In previous worldwide cases, the median time to recovery was 6 weeks (42 days) and the range

was 1 week to 29 months (7–890 days).[9] This difference can be explained by the recent advances in management of AiFVD. The mean time to recovery was shorter in bleeders than in nonbleeders (33.1 ± 45.6 vs. 58.3 ± 76 days; $p < 0.036$), probably because the former group more frequently received antibody eradication therapies than the latter group (81.2 vs. 50.8%, $p < 0.0001$ for prednisolone therapy and 16.7 vs. 5.1%, $p = 0.013$ for the pulse-steroid regimen). In addition, significantly fewer patients in the bleeder group did not receive any antibody-targeted therapies than in the nonbleeder group (10.1 vs. 33.9%, $p < 0.0001$). The prognosis of AiFVD may be related to the underlying diseases, as previously hypothesized.[8,9]

Limitations

This study has several limitations. First, out literature search only included PubMed and ICHUSHI databases, not Scopus, Google Scholar, etc. Second, since the observation periods of patients were generally short, it is difficult to draw any conclusion regarding their long-term prognosis. Third, reports in the abstract form, yielding limited information, were also included. Fourth, many AiFVD-suspected patients were excluded due to the following reasons: they readily responded to FFP administration, their prolonged PT and aPTT were completely corrected in mixing test studies, they were judged to have congenital/hereditary FVD by authors of individual reports, and/or authors did not rule out FV deficiency.[61] Fifth, the mechanism of AiFVD was not explored, as it was beyond the scope of this review.

To overcome some of these limitations, the JCRG started using a database-based registry system, known as the Japanese DID platform (started on February 1, 2021). This system will allow long-term follow-up studies to be conducted to determine the prognosis more precisely and establish optimal second-line therapies for AiFVD.

Conclusion

Because the total number of Japan's AiFVD patients confirmed by JCRG has been steadily increasing (100 in 2017,[62] 164 in 2019,[6] and 201 in 2021 [present study]), this review provides the most up-to-date comprehensive knowledge regarding the Japanese patients with AiFVD. This review had the following findings: (1) based on a population size of 120 million, the incidence of AiFVD in Japan is estimated to be at least 0.04 per million persons per year which is similar to that in Singapore (0.09[8]) and less than that in Australia (0.29,[20] but this report included bovine thrombin–associated cases); (2) the mean age at onset of AiFVD is similar to that of other AiCFDs; (3) AiFVD is predominant among men than women; (4) AiFVD is more severe than previously thought; (5) some patients with AiFVD have very low FV inhibitor titers, suggesting the presence of nonneutralizing and hyperclearance-type anti-FV autoantibodies; (6) as nonneutralizing anti-FV autoantibodies can be overlooked in functional FV inhibitor assays, immunological anti-FV antibody detection is recommended, especially in the absence of FV inhibitor; (7) the hemorrhagic death rate was lower than that reported in previous studies; and (8) the prognosis of AiFVD seemed fairly good.

We hope that the findings of this review will help clinicians face challenges in diagnosing and treating patients with AiFVD.

Authors' Contributions

A.I. initiated and designed the study, extracted data, wrote, edited, and proofread the manuscript. T.O. conducted experimental examinations, statistical analyses, and proofread the manuscript. M.S. performed experimental examinations and proofread the manuscript.

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Conflict of Interest

None declared.

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Appendix A

The Japanese Collaborative Research Group's Nationwide Survey

The Japanese Collaborative Research Group (JCRG) survey, its integrated/unified laboratory tests, and our experimental examinations were approved by the institutional review board of Yamagata University and the individual hospitals of each attending physician. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki.

When a bleeding patient visits a hospital, the physician in charge of the patient consults a hematologist, who then consults the patient and/or reports the patient to our JCRG headquarters. Subsequently, blood samples were collected and sent to a commercial laboratory (SRL Ltd., Hachioji, Japan) and the JCRG headquarters.

Literature Searches

We also performed extensive literature searches at least twice a year in the PubMed (in English) and ICHUSHI (in Japanese) databases. The following search terms were used: (immune) OR (antibody) OR (autoimmune) OR (autoantibody) AND (factor V) OR (factor 5) OR (proaccelerin) OR (labile factor) AND (deficiency) OR (inhibitor) for PubMed and similar Japanese terms for ICHUSHI.

Inclusion and Exclusion

Suspected autoimmune FV deficiency (AiFVD) cases were selected based on the governmental diagnostic criteria of DID (code: 288–4). These criteria were previously enacted by the Japanese MHLW (►**Table 1**) and were analogous to the 2015 criterion for diagnosing AiFXIIID:[10] (1) "definite" diagnosis, when anti-factor (F)-V autoantibodies are detected in blood sample; (2) "probable" diagnosis, when the sample is positive for an FV inhibitor (termed "probable-2" in this article); or (3) when the 1:1 mixing test and/or cross-mixing test using patient's and control's plasma samples (based on prothrombin time [PT] and/or activated partial thromboplastin time [aPTT]) presents an inhibitory but not deficient pattern in the presence of isolated decreased FV activity (FV:C) (termed as "probable-1" in this article); and (4) the remaining suspected AiFVD patients were included in the "possible" group. Patients with congenital and other distinguished acquired FV deficiencies (acFVDs), such as vitamin-K deficiency, FV deficiency due to warfarin treatment, severe liver dysfunction, disseminated intravascular coagulopathy, and other autoimmune coagulation factor deficiencies (AiCFDs), were carefully excluded. AiFVD is not considered congenital FVD if immunosuppressive therapy resulted in normal FV levels or if the patient achieved spontaneous resolution.

Data Collection

The following data were collected from the included patients: sex, age at presentation, bleeding symptoms, underlying diseases, hemoglobin levels, platelet counts, FV:C levels, FV antigen (FV:Ag) levels, presence of anti-FV autoantibody, FV inhibitor levels, and mixing test results based on PT, aPTT, or both. In addition, clinical data, such as data on hemostatic medicines and immunosuppressive agents used, prognosis, and days to recovery (if recovered), were collected. The FV inhibitory potential (pot.) was calculated by subtracting the actual residual FV activity of the 1:1 mixture from the calculated FV activity of the mixture (average FV activity of patient and healthy control) as previously described for FXIII inhibitory potential.[63]

Statistical Analysis

Categorical and continuous variables were compared between the two groups using the Pearson chi-square test and the Kruskal–Wallis test, respectively. Statistical analyses were performed using the JMP software (version 12.2.0; SAS Institute, Cary, NC). Statistical significance was set at $p < 0.05$.

For statistical purposes, FV:C levels or clotting time (PT or aPTT) lower than or higher than the indicated values were considered as the indicated values per se, for example, $<1\%$ as 1% or >100 seconds as 100 seconds, respectively.

Erratum: An erratum has been published for this aricle (DOI: 10.1055/s-0042-1759569).