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Acquired factor V inhibitor: a nation-wide study of 38 patients

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Summary

Acquired factor V inhibitor (AFVI) is an extremely rare disorder that may cause severe bleeding. To identify factors associated with bleeding risk in AFVI patients, a national, multicentre, retrospective study was made including all AFVI patients followed in 21 centres in France between 1988 and 2015. All patients had an isolated factor V (FV) deficiency <50% associated with inhibitor activity. Patients with constitutional FV deficiency and other causes of acquired coagulation FV deficiencies were excluded. The primary outcome was incident bleeding and factors associated with the primary outcome were identified. Thirty-eight (74 [36–100] years, 42·1% females) patients with AFVI were analysed. Bleeding was reported in 18 (47·4%) patients at diagnosis and in three (7·9%) during follow-up (7 [0·2–48.7] months). At diagnosis, FV was <10% in 31 (81·6%) patients. Bleeding at diagnosis was associated with a prolonged prothrombin time that strongly correlated with the AFVI level measured in plasma {$r = 0{\cdot}63$, 95% confidence interval (CI) [0·36–0·80], $P < 0{\cdot}05$}. Bleeding onset during follow-up was associated with a slow AFVI clearance ($P < 0{\cdot}001$). The corresponding receiver operating characteristics curve showed that AFVI clearance was predictive of bleeding onset with an AFVI clearance of seven months with a sensitivity of 100% (95% CI: 29–100) and a specificity of 86% (95% CI: 57–98, $P = 0{\cdot}02$). Kaplan–Meier analysis showed that AFVI clearance >7 months increased the risk of bleeding by 8 (95% CI: [0·67–97], $P = 0{\cdot}075$). Prothrombin time at diagnosis and time for clearance of FV inhibitor during follow-up are both associated with bleeding in patients with AFVI.

Keywords: acquired factor V inhibitor, prothrombin time, factor V inhibitor clearance, bleeding.

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Introduction

Acquired factor V inhibitor (AFVI) is an exceedingly rare entity with an incidence estimated <0·5 per million person years.[1,2] AFVI usually occurs after the sixth decade of life[3] and may be responsible for life-threatening bleeding.[4–6] AFVI may also be fortuitously diagnosed in asymptomatic patients[7,8] or even associated with thrombosis.[9–11] AFVI usually is an IgG antibody directed to the second C-type domain of the light chain of factor V (FV), which is the binding site for phosphatidylserine.[12] The heterogeneous clinical phenotypes may depend on how, according to the specific targeted epitope, anti-FV antibodies affect the balance between pro- and anticoagulant functions.[13–15]

After their description in late 1950s,[16,17] FV inhibitors were described in the setting of surgical exposure to bovine thrombin[18–21] or following transfusion of fresh frozen plasma in patients with severe congenital FV deficiency.[12,22,23] Nowadays, AFVI is mostly drug-induced.[23–25] Treatment of AFVI is empiric and based on corticosteroids or intravenous immunoglobulins (IVIG), and transfusion support in patients with severe bleeding.[3,26] Data regarding the management of AFVI are scarce, however, and mostly based on few case reports.[1,3,23,27–29] To our best knowledge, no study has aimed to stratify the risk of bleeding in AFVI patients. We thus conducted a national multicentre retrospective study to identify factors associated with bleeding in AFVI patients.

Material and methods

Data collection

We retrospectively collected data from patients with AFVI diagnosed between 1988 and 2015 in 21 French hospitals, including 10 cases previously published.[30–35] Physicians were asked by the French Société Nationale Française de Médecine Interne (SNFMI) and the Groupe Français d'études sur l'Hémostase et la Thrombose (GFHT) networks to report cases of AFVI. Patients were included if they fulfilled the following criteria: (i) age over 18 years; and (ii) AFVI diagnosis with isolated FV deficiency <50% on at least two separate occasions associated to specific inhibitor. Exclusion criteria were: (i) constitutional FV deficiency with identified gene mutation; (ii) other causes of acquired coagulation FV deficiencies, such as chronic liver disease or disseminated intravascular coagulation; and (iii) AFVI associated with bovine thrombin. A standardized form was used to retrieve demographic, medical history, laboratory, treatment and follow-up data from medical records.

Biological characterization of acquired factor V inhibitor activity

As previously reported,[36] the clinical laboratory criteria used for diagnosis of a factor V inhibitor included: (i) a prolonged prothrombin time (PT) that did not correct when patient plasma was mixed 1:1 with pooled normal plasma; (ii) a decreased or non-measurable factor V level; and (iii) demonstration of an inhibitor to factor V by modification of the Bethesda method inhibitors.[37] For determination of the factor V inhibitor titers, pooled normal plasma was mixed 1:1 with patient plasma and incubated at 37°C for 2 h. Factor V activity in the patient mixture was then determined and divided by the factor V activity in a control plasma sample, also incubated at 37°C for 2 h. In this assay, one 'inhibitor unit' was defined as the amount inactivating one half of the factor V activity in the patient mixture. Additional laboratory testing, including measurement of thrombin clotting time, factor II, factor VIII, factor X and fibrinogen levels and lupus anticoagulant screening, were performed in some cases. Date of AFVI diagnosis was defined as the day of first identification of FV inhibitor activity.

Primary outcome

The primary outcome was the occurrence of clinically relevant bleeding over follow-up. Bleeding incidents were ascertained, blinded to laboratory data, by physician interview using a standardized questionnaire and through examination of medical records. Clinically relevant bleeding included major bleeding (e.g. bleeding in a critical area or organ such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome), life-threatening bleeding (e.g. bleeding associated with a haemoglobin decrease of 5·0 g/dl, or requiring transfusion of four units of blood or inotropic agents, or bleeding necessitating surgery) and other bleeding severities (e.g. skin haematoma, spontaneous nosebleed, macroscopic haematuria, gastrointestinal bleeding, gingival bleeding, any bleeding leading to hospitalization, any bleeding leading to transfusion <4 units, or any other bleeding considered relevant by the investigator). All bleedings that occurred were considered for analysis. For patients who had more than one bleeding incident, the first event was considered for analysis.

Ethical statement

Our study is a retrospective human non-interventional study where information used in the study was collected for clinical care and epidemiological methods were used to analyse the data. According to the French Public Health Laws, approval from an Institutional Review Board and written consent are not required for human non-interventional studies. Out of ethical considerations, however, patients were informed that data collected in medical records might be used for research study in accordance with the privacy rules. The study's protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. Our study involves personal health data and has been authorized by the Commission Nationale de l'Informatique et des Libertés (CNIL; 2218687v0).

Statistical analysis

Data are expressed as median with range (min–max) for continuous variables, with non-Gaussian distribution and frequency (percentage) for categorical variables. Comparisons were made using Mann–Whitney tests for continuous variables and Fisher tests for categorical variables. The Spearman correlation test was used to determine correlations between variables, with r being the Spearman correlation coefficient. The Kaplan–Meier method was used to represent bleeding onset during follow-up in asymptomatic patients at diagnosis according to the AFVI clearance (i.e. more or less than seven months). Two-sided P values of <0·05 were considered to indicate statistical significance. Statistical analyses were performed with GraphPad Prism 5.01 software (GraphPad Software, San Diego, CA, USA).

Results

Patient characteristics

Forty patients with AFVI followed in 21 centres were identified in France between 1988 and 2015. A diagnosis of AFVI was made after 2000 in all but three patients (92·5%). AFVI-presenting manifestation was bleeding in 18 cases (45%). Conversely, 22 patients had no bleeding at AFVI diagnosis. In those cases, AFVI was fortuitously discovered on the basis of routine laboratory investigations (n = 20) or diagnosed in the setting of venous thromboembolism (VTE, n = 2). Thirty-eight patients (74 [36–100] years, 16 (42·1%) females) were considered for further analysis after exclusion of patients with VTE.

At AFVI diagnosis, comorbidities (such as smoking, high blood pressure, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease and/or strokes) and associated conditions (such as HIV infection, malignancy, inflammatory disease or antibiotics exposure) were observed in 86·8% (n = 33) and 73·7% (n = 28) of cases, respectively (Table I). Exposure to antibiotics was reported in 22 (57·9%) patients. Antibiotics were beta-lactams in most cases (n = 16, 72·7%) and were administered a median of 16 [4–60] days before AFVI diagnosis (Table SI).

Bleeding at AFVI diagnosis

Clinically relevant bleeding at onset occurred in 18 patients including muscle haematoma (n = 7), spontaneous epistaxis (n = 5), gingival bleeding (n = 3), macroscopic haematuria (n = 2), gastrointestinal bleeding (n = 2), uterine bleeding (n = 1) and purpura (n = 1). Two patients had major bleeding [i.e. intracranial (n = 1) and retroperitoneal (n = 1)] and one had life-threatening bleeding. Red-cell transfusion, fresh frozen plasma transfusion, platelet transfusion and/or vitamin K administration were required in 11 (61·1%), 7 (38·9%), 3 (16·7%) and 2 (11·1%) cases, respectively. In addition, steroids were administered in 14 (77·8%) patients. Seven (38·9%) and four (22·2%) patients received IVIG and/or immunosuppressive drugs, respectively. Immunosuppressive drugs were azathioprine (n = 1), cyclophosphamide (n = 1) or rituximab (n = 2). Fatal bleeding — uncontrolled haemoptysis — occurred six days after diagnosis in only one case. Among bleeding patients, three patients died during a median follow-up of 4·5 [0·2–24.3] months after AFVI diagnosis, but the cause of death was directly ascribed to AFVI in only one case (i.e. fatal haemoptysis).

At AFVI diagnosis, prolonged PT inversely correlated with FV levels (Figure S1) and was significantly associated with bleeding (52 [19–79] vs. 35 [16–67] s, P < 0·05; Table 1). In addition, the level of AFVI in plasma tended to be higher in bleeding patients {38·8 [0·4–300] vs. 13·4 [0·4–71] Bethesda units (BU), P = 0·08} and correlated positively with PT (r = 0·63, 95% CI [0·36–0·80], P < 0·05; Fig 1A) and inversely with FV levels (r = −0·43, 95% CI [−0·71 to −0·03], P < 0·05; Fig 1B).

Bleeding during follow-up

Twenty patients were asymptomatic at AFVI diagnosis. Despite no bleeding, eight (40%) patients received steroids and/or IVIG at diagnosis. During follow-up, bleeding — macroscopic haematuria (n = 1), intracranial (n = 1) or gastrointestinal bleeding (n = 1) — occurred in three patients 1, 12 and 12·5 months after AFVI diagnosis. Level of FV in plasma at bleeding time was <2% in all three cases. Treatment of bleeding required red-cell transfusion in two patients associated with IVIG in one. No relapse occurred. During a median follow-up of eight [3 to 48.7] months after AFVI diagnosis, three of these patients died but death was not ascribed to AFVI.

Age, sex, comorbidity, associated conditions, and treatment received at first diagnosis did not differ between patients bleeding during follow-up and those who remained asymptomatic (Table II). Interestingly, a higher AFVI level at diagnosis (35·7 [0·4–71] vs. 5·5 [0·4–47] BU, P = 0·09) and a dramatically slow AFVI clearance (12 [8-48.7] vs. 2 [0·2–24.3] months, P = <0·001) were both associated with bleeding during follow-up. The corresponding receiver operating characteristics curve demonstrated that AFVI clearance was predictive of bleeding onset with an AFVI clearance >7 months showing a sensitivity of 100% (95% CI: 29–100) and a specificity of 86% (95% CI: 57–98), P = 0·02 (Figure S2). In Kaplan–Meier analysis, AFVI clearance >7 months was associated with bleeding onset (HR 8; 95% CI [0·67–97], P = 0·075; Figure 2). The only factor associated with AFVI clearance <7 months was antibiotic exposure (Table SII).

Discussion

We show in this national multicentre retrospective study that PT at diagnosis and clearance of FV inhibitor during follow-up are associated with incident bleeding in AFVI.

Table I. Factors associated with bleeding at AFVI diagnosis.

Factor	All $n = 38$	Bleeding $n = 18$	Asymptomatic* $n = 20$	$P^{\dagger}$
Age, years	74 [36–100]	74 [36–100]	73·5 [40–92]	ns
Female sex, *n* (%)	16 (42·1)	8 (44·4)	8 (40)	ns
Comorbid conditions, *n* (%)				
Smoking	9 (23·7)	4 (22·2)	5 (25)	ns
High blood pressure	20 (52·6)	13 (72·2)	7 (35)	<0·05
Diabetes mellitus	9 (23·7)	6 (33·3)	3 (15)	ns
CAD	6 (15·8)	3 (16·7)	3 (15)	ns
COPD	1 (2·6)	0 (0)	1 (5)	ns
Strokes	4 (10·5)	1 (5·5)	3 (15)	ns
Antiplatelet treatment	6 (15·8)	2 (11·1)	4 (20)	ns
Anticoagulant treatment	3 (7·9)	2 (11·1)	1 (5)	ns
Antiplatelet + anticoagulant	3 (7·9)	1 (5·5)	2 (10)	ns
Associated conditions, *n* (%)				
HIV infection	1 (2·6)	1 (5·5)	0 (0)	ns
Malignancy	3 (7·9)	2 (11·1)	1 (5)	ns
Inflammatory diseases	2 (5·3)	1 (5·5)	1 (5)	ns
Antibiotics exposure	22 (57·9)	9 (50)	13 (65)	ns
Biological features				
Haemoglobin, g/d	9·7 [6·6–14.5]	9·6 [6·6–12]	11·6 [8·2–14.5]	<0·01
Platelet, G/	229 [51–355]	222·5 [51–326]	244·5 [135–355]	ns
PT, s	46 [16–79]	52 [19–79]	35 [16–67]	<0·05
FV < 10%, *n* (%)	31 (81·6)	15 (83·3)	16 (80)	ns
AFVI (mean, BU)	25·5 [0·4–300]	38·8 [0·4–300]	13·4 [0·4–71]	0·08
Treatment at diagnosis, *n* (%)				
Corticosteroid	18 (47·4)	14 (77·8)	4 (20)	<0·001
IVIG	11 (28·9)	7 (38·9)	4 (20)	ns
Immunosuppressive drugs	4 (10·5)	4 (22·2)	0 (0)	ns
Corticosteroid + IVIG	6 (15·8)	5 (27·8)	1 (5)	ns
Corticosteroid + IVIG + IS	2 (5·3)	2 (11·1)	0	ns
Follow-up[‡]				
Length, m	7 [0·2–48.7]	4·5 [0·2–24.3]	8 [3–48.7]	ns
AFVI clearance (median, m)	1·2 [0·2–48.7]	1 [0·2–24]	3·77 [0·2−48.7]	0·05
Death, *n* (%)	6 (15·8)	3 (16·7)	3 (15)	ns

Malignancy included advanced myelodysplastic syndrome ($n = 1$) and colon cancer ($n = 2$) Inflammatory disease included psoriasis ($n = 1$) and inflammatory bowel disease ($n = 1$).

AFVI, acquired factor V inhibitor; BU, Bethesda unit; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; FV, factor V; HIV, human immunodeficiency virus; IS, immunosuppressive; IVIG, intravenous immunoglobulin; PT, prothrombin time; s, second; m, months.

*Two patients with venous thromboembolism at AFVI diagnosis were excluded from the analysis. In both cases, lupus anticoagulant testing was negative.

[†]Between bleeding and asymptomatic, univariate analysis.

[‡]Follow-up analysed in 33/38 patients (two lost to follow-up, three deaths during the first two weeks).

Our study largely confirmed that AFVI occurs primarily in the elderly, which clearly differentiates this condition from hereditary forms of FV deficiency.[38] Accordingly, most patients suffered comorbidities including high blood pressure, diabetes mellitus and coronary artery disease, as previously reported.[39] In our study, almost half of the AFVI patients were asymptomatic which strikingly differs from previous reports.[1,3,23,28,29] This might be explained by a reporting bias since cases were selected through two national networks, including biologists. AFVI was indeed fortuitously discovered on routine laboratory investigations in half of the patients. On the other hand, major bleeding occurred in 15% of patients that were asymptomatic at diagnosis.

In contrast with smaller studies with limited power,[21,23,29] we were able to show a statistically significant association between PT and bleeding at diagnosis. Moreover, PT strongly correlated with the FV inhibitor activity measured in plasma and thus appears to reflect the FV inhibition by the antibodies. Being a routine biological test, PT is a practical tool for the clinician to assess the risk of bleeding in the setting of

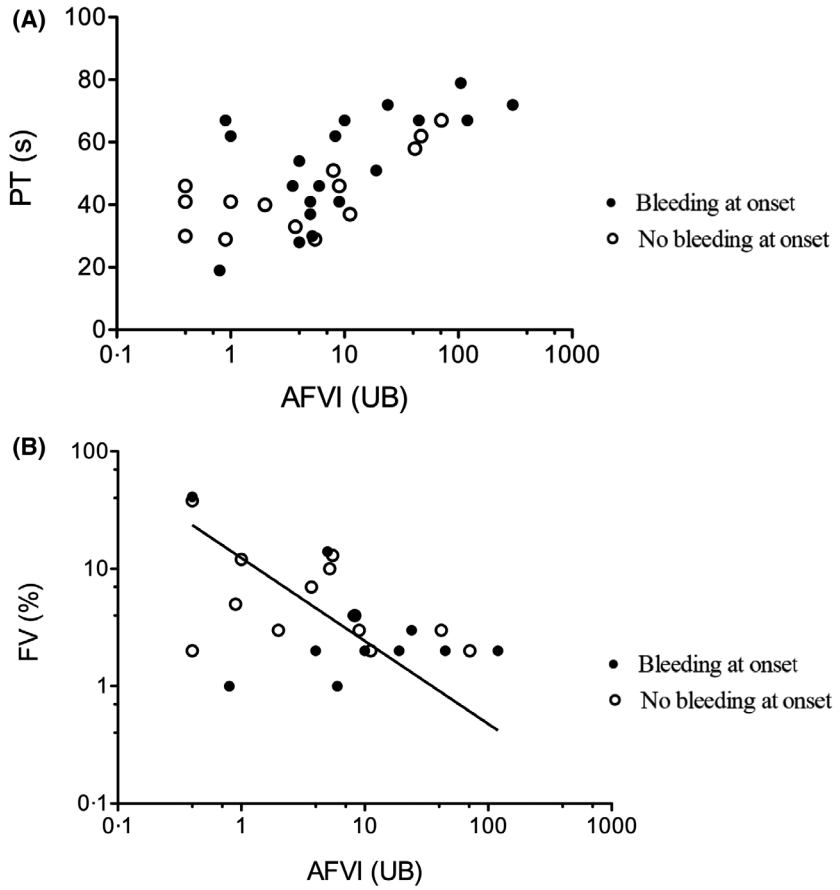

Fig 1. Correlation of factor V inhibitor activity with prothrombin time and factor V level. (A) Acquired factor V inhibitor (AFVI) level correlated with prothrombin time (PT; $r = 0{\cdot}52$, 95% confidence interval (CI) [0·22–0·73], $P < 0{\cdot}05$). Analysis was performed on 34 patients. (B) AFVI level inversely correlated with FV levels ($r = -0{\cdot}43$, 95% CI [−0·71 to −0·03], $P < 0{\cdot}05$). Analysis was performed on 26 patients.

care. In patients who were first asymptomatic, the longer the exposition to the inhibitor, the higher was the risk of bleeding over time.

Antibiotics treatment, mainly beta-lactams — including third-generation cephalosporin and penicillin — was the most frequent triggering condition, as reported previously.[1,3,23,27,28] Antibiotics may combine with or alter FV which becomes antigenic.[5] The fact that AFVI occurs at a median of 16 days after treatment initiation argues against a causal role for infection, which is usually controlled at this time. As in previous reports,[23] we emphasize the importance of removing the triggering factor as soon as possible.

Besides antibiotic exposure, no other factor at diagnosis was associated with the forthcoming AFVI clearance. However, it should be pointed out that: (i) AFVI clearance tended to be shorter in patients who received inhibitor elimination therapy (IET) — including steroids, IVIG and/or immunosuppressive (IS) drugs — as compared to those who did not (1 [0·2–48.7] vs. 2 [0·2–12] months, P = 0·46); (ii)-no bleeding occurred during follow-up in asymptomatic patients who received IET at AFVI diagnosis; and (iii) bleeding occurred only in patients who did not receive IET at diagnosis. Moreover, because IET was more frequently given in bleeding patients at AFVI diagnosis, the shorter AFVI clearance in those patients (1 [0·2–24] vs. 3·77 [0·2–48.7] months, $P = 0{\cdot}05$) may indicate IET efficacy. Because of the small number of patients, no efficacy analysis for a specific IET drug could be performed.

Our study has limitations inherent to its small size and retrospective scheme. Because of its selection process, through national networks of both clinicians and biologists, many of our AFVI cases were asymptomatic. Such a series might however more accurately reflect the 'real life' management of AFVI patients. Although lupus anticoagulants (LA) have been reported to occasionally present like pseudo-factor inhibitors,[40] LA testing was not available in most cases ($n = 26$). However antiphospholipid antibodies (including LA, anticardiolipin and anti-$\beta_2$glycoprotein-1 antibodies) testing was always negative when performed ($n = 12$), bleeding ($n = 21$) and prolonged PT ($n = 38$) are not considered classical features of the antiphospholipid syndrome[41] and titration of AFVI was high in most cases and strongly

Table II. Factors associated with bleeding during follow-up.

Factor	Diagnosis Asymptomatic $n = 20$	Follow-up Bleeding $n = 3$	Follow-up No bleeding $n = 17$	P*
Age, years	73·5 [40–92]	73 [70–85]	74 [40–92]	ns
Female sex, *n* (%)	8 (40)	0 (0)	8 (47·1)	ns
Comorbid conditions, *n* (%)				
Smoking	5 (25)	0 (0)	5 (29·4)	ns
High blood pressure	7 (35)	0 (0)	7 (41·1)	ns
Diabetes mellitus	3 (15)	1 (33·3)	2 (11·8)	ns
CAD	3 (15)	1 (33·3)	2 (11·8)	ns
COPD	1 (5)	1 (33·3)	0 (0)	ns
Strokes	3 (15)	0 (0)	3 (17·6)	ns
Antiplatelet treatment	4 (20)	1 (33·3)	3 (17·6)	ns
Anticoagulant treatment	1 (5)	0 (0)	1 (5·9)	ns
Antiplatelet + anticoagulant	2 (10)	0 (0)	2 (11·8)	ns
Associated conditions, *n* (%)				
HIV infection	0 (0)	0 (0)	0 (0)	-
Malignancy	1 (5)	0 (0)	1 (5·9)	ns
Inflammatory diseases	1 (5)	0 (0)	1 (5·9)	ns
Antibiotics exposure	13 (65)	0 (0)	13 (76·5)	<0·05
Biological features at diagnosis†				
PT, s	35 [16–67]	30 [16–67]	41 [25–62]	ns
FV < 10%, *n* (%)	16 (80)	2 (66·7)	14 (82·5)	ns
AFVI level, BU mean	13·4 [0·4–71]	35·7 [0·4–71]	5·5 [0·4–47]	0·09
Treatment at diagnosis† *n* (%)				
Corticosteroid	4 (20)	0 (0)	4 (23·5)	ns
IVIG	4 (20)	0 (0)	4 (23·5)	ns
Immunosuppressive drugs	0 (0)	0 (0)	0 (0)	-
Corticosteroid + IVIG	1 (5)	0 (0)	1 (5·9)	ns
Corticosteroid + IVIG + IS drugs	0 (0)	0 (0)	0 (0)	-
Antiplatelet withdrawal	0 (0)	0 (0)	0 (0)	-
Anticoagulant withdrawal	1 (5)	0 (0)	1 (5·9)	ns
Antibiotics withdrawal	13/13 (100)	-	13/13 (100)	-
Follow-up‡				
Length, months	8 [3–48.7]	12 [8–48.7]	8 [3–24.3]	ns
AFVI clearance (median, m)	3·77 [0·2–48.7]	12 [8–48.7]	2 [0·2–24.3]	<0·001
Death, *n* (%)	3 (15)	0 (0)	3 (17·6)	ns

AFVI, acquired factor V inhibitor; BU, Bethesda unit; CAD, coronary artery disease; COPD chronic obstruction pulmonary disease; FV, factor V; HIV, human immunodeficiency virus; IS, immunosuppressive; IVIG, intravenous immunoglobulin; PT, prothrombin time; s, second; m, months.
*Between bleeding and no bleeding, univariate analysis.
†Biological features and treatment received at AFVI diagnosis while all asymptomatic.
‡Analysed in 17/20 patients (two lost to follow-up, one death during the first week).

correlated with PT and FV. Eventually, our study is the largest reported multicentre series of AFVI and its extended follow-up strikingly contrasts with previous reports.[1,3,23,27,28]

In conclusion, PT at diagnosis and clearance of FV inhibitor during follow-up are both biological markers that may help clinicians to better stratify bleeding risk in AFVI patients.

Conflicts of interest

The authors report no conflicts of interest.

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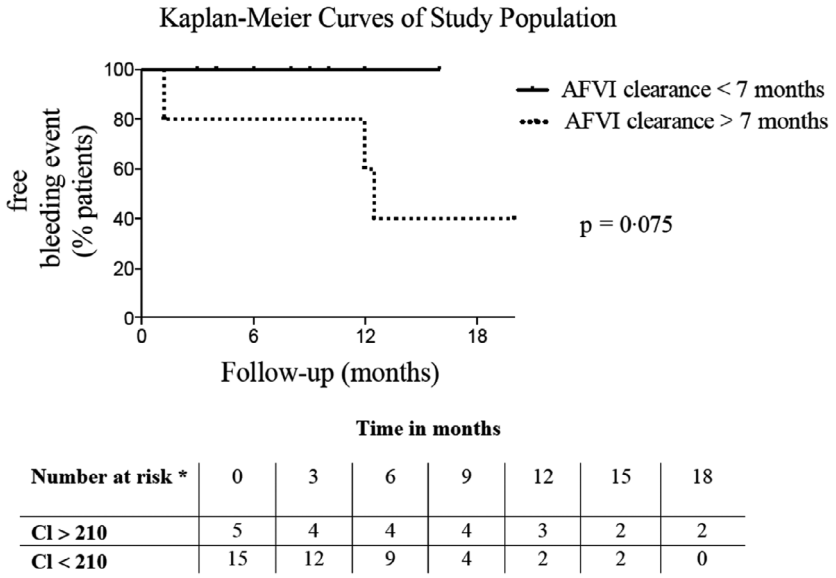
Author contributions

TG had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. TG and TP conceived the project. TG, CV, DF, NA, KS and TP interpreted and analysed the data.



Time in months

Number at risk *	0	3	6	9	12	15	18
Cl > 210	5	4	4	4	3	2	2
Cl < 210	15	12	9	4	2	2	0

Fig 2. Kaplan–Meier curves of study population. Patients with acquired factor V inhibitor (AFVI) clearance >7months had higher rates of bleeding onset during follow-up than patients with AFVI clearance <7months (HR 8; 95% confidence interval (CI) [0·67–97], $P = 0·075$).

TG, CV, DF, NA, ED, AD, CF, CJ, ER, LR and NS selected appropriate subjects for analysis and provided clinical data. TG, CV, DF, NA, ED, AD, CF, CJ, ER, LR, and NS helped to analyse data and to write the paper. TG, KS and TP wrote the manuscript. All authors have read and approved the manuscript for publication.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Fig S1. Prothrombin time and factor V level.

Fig S2. Receiver operating characteristics (ROC) curve of acquired factor V inhibitor (AFVI) clearance for prediction of bleeding.

Table SI. Antibiotic exposition in acquired factor V inhibitor (AFVI) patients.

Table SII. Factors associated with acquired factor V inhibitor (AFVI) clearance in asymptomatic patients.

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Appendix 1. List of collaborators (RAVI study group) to be added in pubmed

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