Received: 17 January 2026 | Accepted: 6 July 2026

DOI: 10.1002/hem3.70451

ARTICLE

HemaSphere eha

An Italian cartography of VEXAS-related thrombosis

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Abstract

Thrombotic events (TEs) occur in up to 40% of patients with vacuoles, E1 enzyme, X-linked, autoinflammatory, and somatic (VEXAS) syndrome, but data on its clinical-genomics features and anticoagulation strategies are limited. To gain more insight into this, we conducted a two-step study evaluating the prevalence and outcome of TE in VEXAS. First, among 1086 patients followed for TEs, 198 were men aged >40 years with unprovoked thrombosis and no known thrombophilia; 21 also had at least one VEXAS-compatible feature and underwent *UBA1* exon 3 testing. No *UBA1* mutation was detected in these 21 patients. Next, we leveraged our Italian VEXAS network, and we accrued 87 molecularly confirmed Italian VEXAS cases (median age 70 years). Any history of TE was documented in 43/87 patients (49%), deep vein thrombosis being the most common (71%). Because follow-up varied, incident thrombosis was analyzed using a time-to-first-event framework from molecular VEXAS diagnosis, with death without prior TE treated as a competing event. Among 49 patients without prior/concomitant TE, five developed incident post-diagnosis TE; the 24-month cumulative incidence was 18.3%. Thrombophilia testing revealed a 15% co-occurrence, including heterozygous Factor V Leiden, Factor II G20210A, and anti-cardiolipin antibodies. Treatments comprised direct oral anticoagulants (DOACs) (51%), low molecular weight heparin (LMWH) (28%), Fondaparinux (14%), and vitamin K antagonists (AVKs) (7%). Notably, 27% experienced multiple TEs, of which 22% occurring despite anticoagulation during disease flares. Our findings provide an updated cartography of VEXAS-related TE, suggesting early screening for thrombophilia in these patients to inform both personalized anticoagulation and disease-control strategies.

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INTRODUCTION

VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, and somatic) syndrome is a severe adult-onset autoinflammatory disorder caused by somatic mutations of the X-linked *UBA1* gene.[1] Such alterations perturb cellular ubiquitylation processes ultimately causing hyperinflammation, generating a fertile soil for acquisition of additional somatic myeloid gene mutations.[2] From a hematological standpoint, VEXAS patients typically present with myelodysplastic syndrome/neoplasms (MDS), macrocytic anemia (regardless of an overt MDS diagnosis), and plasma cell dyscrasia.[3] On the other hand, inflammatory manifestations linked to the hypercytokinemia encompass skin (Sweet syndrome or Sweet syndrome-like lesions), joints, lung, gastrointestinal, ocular and kidney involvement, as well as noninfectious fever, nose and ear chondritis.[4]

As a result of such pro-inflammatory state, thrombotic events (TEs) are one of the most recurrent disease manifestations, inherently linked to the VEXAS' morbidity.[5,6] TE may occur early in the disease course with later recurrence, negatively impacting a patient's quality of life and survival outcome.[7] Previous studies have reported a high incidence of TE, typically ranging from 14% to 40%,[8,9] with a notable proclivity to venous thromboembolism (VTE) over arterial thrombosis.[10] Chronic inflammation leads to a prothrombotic state via various mechanisms: inflammatory cytokines (particularly IL-6 and TNF-α) induce the expression of tissue factor on monocytes and endothelial cells, activating the coagulation cascade.[11] At the same time, inflammation causes endothelial dysfunction, with the acquisition of a pro-adhesive and prothrombotic phenotype.[11,12] Furthermore, activated neutrophils can release "extracellular traps" (NETs), which act as scaffolds for the formation of thrombi, while activated platelets further amplify the inflammatory and coagulative response.[13,14] It should be noted that little is known about the concomitant presence of antiphospholipid antibodies, for example, anti-cardiolipin (aCL) and anti-β_2-glycoprotein I (anti-β_2GPI) in VEXAS and VEXAS-related TE.

So far, the clinical features harbinger of increased thrombotic risk and the optimal management strategies for recurrence remain poorly defined in VEXAS.[15] Given the lack of robust epidemiological data, we decided to undertake a multicenter, national study devising a two-step strategy. Specifically, we aimed to establish a detailed cartography of VEXAS-associated TE, focusing on prevalence, identification of clinical predictors for thrombosis, and analyzing recurrence patterns and management outcomes over 232 patient-years of observation.

METHODS

Study cohort and design

We designed a two-phase study to investigate the link between VEXAS syndrome and thromboembolism. The first phase consisted of a cross-sectional pilot study, with the aim of estimating the prevalence of *UBA1* mutations in an unselected population followed for thrombosis. We analyzed 1086 patients attending the Hemostasis and Thrombosis Clinic at Tor Vergata Polyclinic in Rome, Italy. From this population, 198 subjects were selected based on the typical demographic criteria of VEXAS (male, age >40 years) and clinical criteria (history of at least one unprovoked venous or arterial TE event, in the absence of known thrombophilia). Subsequently, further screening was based on the presence of at least one clinical manifestation suggestive of VEXAS syndrome. All clinical and laboratory features recognized as consistent with VEXAS were considered; a patient was included if at least one feature was present, such as macrocytic anemia and/or rheumatological disorders. This screening led to the identification of 21 patients. These were subjected to targeted molecular screening for the *UBA1* gene. Sanger sequencing of exon 3 was used to detect the canonical VEXAS mutations, in accordance with already described protocols.[4] The second phase of the study leveraged a national multicenter cohort, from a collaborative network of clinical sites specializing in the management of patients with VEXAS syndrome. Recruitment took place between January and April 2025, through the dissemination of a link to an electronic database. Between January and April 2025, data were collected via a data entry anonymized format. All cases where a diagnosis of VEXAS syndrome was confirmed both clinically and through molecular analysis, that is, the presence of a pathogenic somatic mutation in *UBA1*, were included. Participating centers could enter all available patients with clinically suspected and molecularly

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confirmed VEXAS syndrome diagnosed and/or managed at their institution before database lock, including deceased patients when sufficient data were available. Through this network, a cohort of 87 male patients was accrued, for a total of 232 patient-years of observation. Information was collected on the following: demographic and clinical characteristics at the time of diagnosis, main laboratory parameters, and VEXAS phenotype (e.g., systemic symptoms, skin or lung involvement, among others). The specific *UBA1* genotype (e.g., p.Met41Val, p.Met41Leu, and p.Met41Thr, among others) was also recorded. For TE, the type (venous vs. arterial), location (e.g., deep vein thrombosis, pulmonary embolism, and myocardial infarction), onset relative to the diagnosis of VEXAS syndrome, and anticoagulant therapy were documented. The molecular diagnosis was confirmed in all patients through screening for the *UBA1* gene, at least of the exon 3, as previously shown.[2,16] Co-diagnosis of MDS was established based on WHO 2022 criteria.[17] Testing for concomitant presence of antiphospholipid antibodies was assessed at TE onset and after 12 weeks as per established guidelines.[18]

All patients provided their written informed consent for the use of their data for research purposes, in accordance with the requirements of the local ethics committees of each participating institution. The entire study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Statistical analysis

Continuous variables were compared using Student's *t*-test or the Mann–Whitney *U* test, and categorical variables were analyzed using Fisher's exact test. Survival was defined as the time from diagnosis to last follow-up or death for any cause and was calculated using Kaplan–Meier estimation. For the longitudinal analysis, follow-up began at molecular VEXAS diagnosis. For the evaluation of cumulative incidence, patients who experienced a TE after a diagnosis of VEXAS syndrome were included. Patients with thrombosis documented before or on the diagnosis date, and patients with TE history but unavailable TE date, were described separately and were not included in the first incident TE risk set. Among patients without prior/concomitant TE, time to first incident TE was calculated from VEXAS diagnosis to TE, death without prior TE, or last follow-up. Death without prior TE was treated as a competing event using cumulative-incidence methods. Because of the limited number of incident events, covariate modeling was considered exploratory and was not used to support predictor claims. Competing events (deceased without thrombosis) and censoring (living without thrombosis) were accounted for using the Fine-Gray method (cuminc function in R studio). A significance level of $P < 0.05$ was considered statistically significant. All analyses and data visualization were generated using the statistical computing environment R (4.0.0R Core Team, R Foundation for Statistical Computing, Vienna, Austria), Excel Microsoft Office 365, and GraphPad Prism (8.4.0).

RESULTS

Step I: The "Tor Vergata" pilot study

The initial phase of our work consisted of a pilot study aimed at investigating the prevalence of VEXAS syndrome in a clinical setting characterized by the development of thrombosis (Figure 1A). By analyzing a cohort of 1086 patients attending the Hemostasis and Thrombosis Clinic at the Tor Vergata Hospital, 198 men over the age of 40 years with a history of venous or arterial TE, classified as idiopathic, were identified. Subsequently, by applying a more stringent criterion based on the concomitant presence of at least one clinical manifestation suggestive of VEXAS syndrome (such as anemia or rheumatological disorders), 21 patients were selected as candidates for molecular analysis. However, none of these subjects was found to be a carrier of somatic mutations in the *UBA1* gene, suggesting that the mere presence of TE without a more pervasive VEXAS-related clinical picture is not sufficient to trigger molecular testing.

Step II: The Italian VEXAS cohort

Clinical and molecular features

The second phase of the study leveraged the Italian VEXAS network accruing 87 patients, all males, with a median age at diagnosis of 70 years (interquartile range, IQR 64–76). Baseline characteristics of the study cohort are detailed in Table 1. The clinical picture at the time of diagnosis was markedly heterogeneous. All patients presented with anemia (median hemoglobin value 9.8 g/dL, IQR = 8.4–11.4) and macrocytosis (median mean corpuscular volume [MCV] value 102.9 fL, IQR = 96.0–108.0). Bone marrow vacuoles were observed in most cases with available marrow evaluation (84%). Overall, 41% of patients ($n = 36$) presented with systemic symptoms, such as fever of unknown origin (FUO) or clinical pictures mimicking conditions such as Still's disease, vasculitis, or systemic lupus erythematosus. Skin involvement, mainly in the form of rash, erythema nodosum, or orbital cellulitis, was present in 39% of cases ($n = 34$). Up to 10% ($n = 9$) of patients had pulmonary involvement, with evidence of multiple consolidations or interstitial pneumonia. Other recurrent clinical manifestations included polychondritis, arthritis, and scleritis. From a hematological perspective, the majority of patients (56%, $n = 49$) had a co-diagnosis of MDS, while 37% ($n = 32$) also showed a monoclonal gammopathy of undetermined significance (MGUS), and only one patient had multiple myeloma. During the course of their disease, 15% of the patients ($n = 13$) did not receive specific VEXAS-specific therapy, 25% ($n = 22$) were treated with glucocorticoids alone, and the remaining 60% ($n = 52$) received glucocorticoids plus at least one additional VEXAS-directed agent. Specifically, 30% ($n = 26$) of patients received at least one bDMARD ($n = 12$ received more than two lines), 37% ($n = 32$) received at least one cDMARD, 18% ($n = 16$) received at least one JAK inhibitor, and 3% ($n = 3$) of patients were treated with azacitidine.

Genotype analysis revealed a typical distribution of somatic variants of the *UBA1* gene. The p.Met41Thr mutation was the most frequent, identified in 40% of the cohort ($n = 35$), followed by p.Met41Val in 29% of patients ($n = 25$), and p.Met41Leu in 7% ($n = 6$). The remaining 24% ($n = 21$) were carriers of other, rarer, mutations of the *UBA1* gene. This subgroup mainly consisted of two categories: splicing site or intronic mutations, such as c.118-1G>A, and missense mutations outside the Met41 codon, such as p.Ser56Phe.

Characteristics of thrombotic events

Episodes of TE were observed in 43 (49%) patients (Figure 1B), with 29 (33%) of them occurring concomitant with the diagnosis of VEXAS syndrome: 35 had a TE before or on molecular VEXAS diagnosis, and 3 TE-positive patients had no analyzable TE date; the latter group was retained for descriptive TE-history analyses but excluded from the first incident post-diagnosis TEs risk set. A particularly significant finding is the high rate of recurrence. Indeed, among 43 patients developing thrombosis, we recorded a total of 59 TE, resulting in a median of 1 event per patient. Fifty-seven (97%) events happened in the venous district, with only 2 (3%) being classified as arterial. The

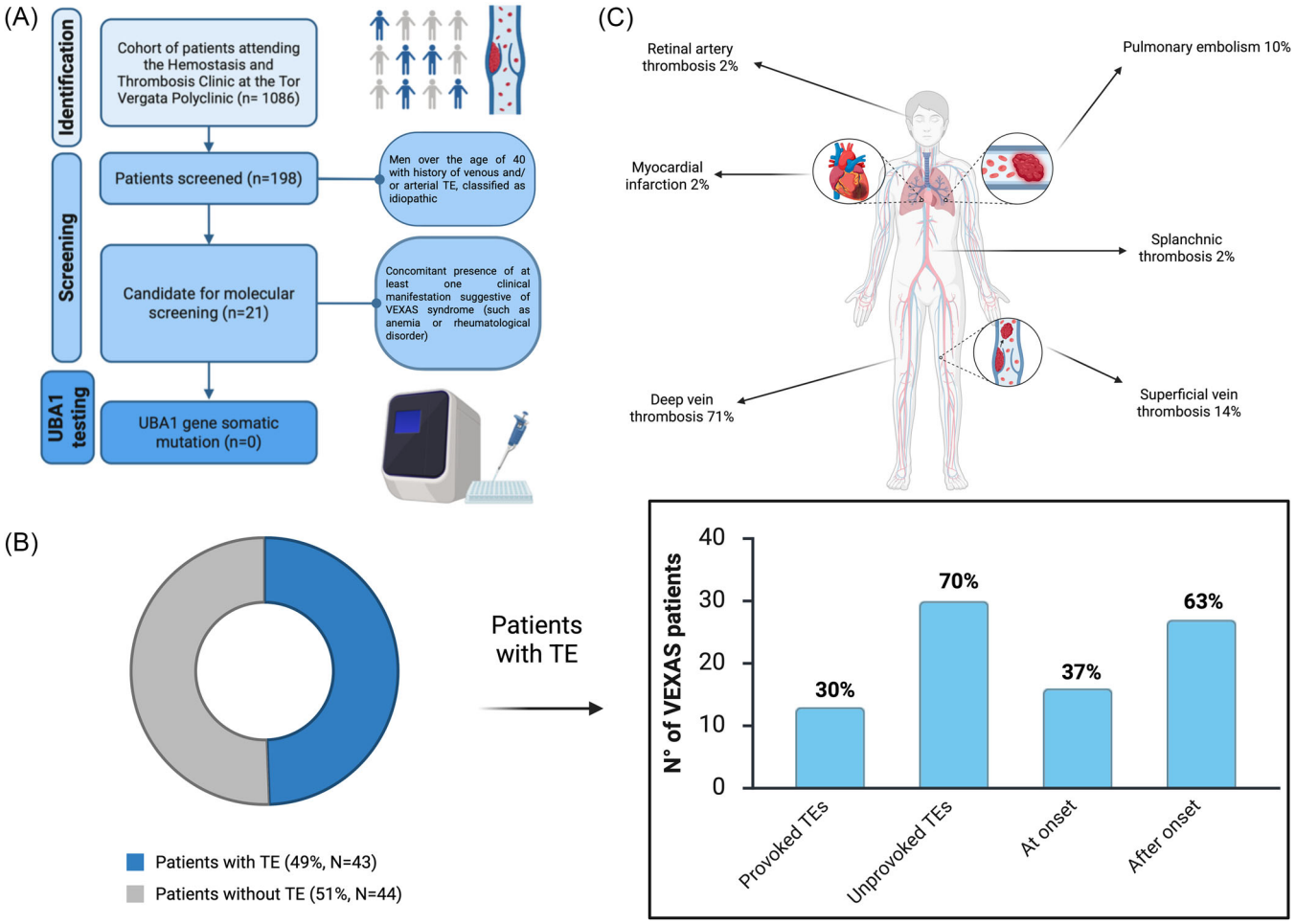

FIGURE 1 **A two-step study of vacuoles, E1 enzyme, X-linked, autoinflammatory, and somatic (VEXAS)-related thrombosis.** In a first part **(A)**, we designed a pilot study (the "Tor Vergata" step) aimed at investigating the prevalence of VEXAS syndrome in a clinical setting characterized by the development of thrombosis. Subsequently, we leveraged our Italian VEXAS patients cohort, evaluating the incidence and characteristics of thrombosis in this setting of patients. **(B)** Donut chart illustrating the percentage of VEXAS patients affected by thrombosis, including a breakdown of the nature of thrombotic events (TEs) and the timing of incidence ("at onset of first clinical manifestation of VEXAS" and "after onset of first clinical manifestation of VEXAS"). In panel **(C)**, the distribution of all TEs based on their localization is presented.

anatomical mapping of such TE (Figure 1C) showed a predominance of deep vein thrombosis in the lower limbs, which accounted for 71% of all TE, followed by superficial venous thrombosis (14%). There were 2 instances of splanchnic venous thrombosis (2%), 1 (2%) case of retinal artery thrombosis and 1 (2%) acute coronary syndrome. The incident risk set included 49 patients, of whom 5 developed first TE after VEXAS diagnosis, 8 deceased without prior TE, and 36 were censored without TE. Median follow-up in this risk set was 13.4 months (IQR, 3.6–23.3), and the 24-month cumulative incidence of first post-diagnosis TE was 18.3% (95% CI 3.9%–35.7%; Figure 2).

Associations with thrombotic events

In order to identify potential clinical associations with thrombosis, we compared the baseline characteristics of patients who experienced TEs (TE group, $n = 43$) with those of patients who did not experience TEs (non-TE group, $n = 44$; Table S1, see also Supplemental Material). Recurrent chondritis (mostly affecting the ear) was more common in the group of patients with thromboembolism (19%) than in those who did not experience thrombosis (2%). Differences in frequency between the two groups were not statistically significant for all other clinical and molecular features analyzed.

While it is difficult to disentangle the relation of thrombosis development and specific therapy, given that most patients (>50%) received multiple lines of treatment and steroids were used in a heterogeneous duration/dosage fashion, 27% ($n = 22$) of cases experienced at least one TE, among patients treated with glucocorticoids alone. In patients treated with glucocorticoids plus a JAK inhibitor, without either bDMARDs or cDMARDs ($n = 7$ patients), two experienced a TE, whereas in the group treated with glucocorticoids plus Azacitidine, one out of three patients developed a TE. Furthermore, 31% of patients ($n = 27$) received ESAs: among these, 41% ($n = 11$) experienced at least one TE (eight VTEs, two arterial events, and one patient with both venous and arterial events). The remaining 69% ($n = 60$) have never received ESAs, and among them 53% ($n = 32$) experienced at least 1 TE (26 VTEs and 6 arterial events).

To assess the contribution of a pre-existing predisposition to thrombosis, the prevalence of common hereditary and acquired thrombophilic risk factors was analyzed (Figure 3A). First, the results showed an extremely low frequency of testing for such alterations in the VEXAS cohort (26%, $n = 23$), despite the high rate of TE and need

for treatment decision. Among these 23 tested cases, $n = 3$ patients were heterozygous for Factor V Leiden, and $n = 1$ for the G20210A mutation of Factor II. A positive status for aCL was found in only $n = 4$ cases, and for anti-β_2GPI in $n = 1$ case. More specifically, in this subset of patients, two patients showed persistent positivity after retesting at 12 weeks. In the first case, the patient maintained positivity for aCL IgG, prompting clinicians to switch anticoagulation to vitamin K antagonist (AVK). In the second case, the patient exhibited persistent aCL IgG positivity accompanied by seroreversion of aβ_2GPI IgG, but the anticoagulation strategy (direct oral anticoagulant [DOAC]) was not modified. Among the remaining patients, one showed a single positive antiphospholipid antibody test that spontaneously became negative, whereas in the other two cases we observed low-level positivity that clinicians did not consider clinically meaningful or worth serial monitoring, given TE resolution under low molecular weight heparin (LMWH) and DOAC, respectively.

TABLE 1 Characteristics of vacuoles, E1 enzyme, X-linked, autoinflammatory, and somatic (VEXAS) population.

Characteristics of VEXAS population	Overall ($n = 87$)
Demographics	
Age at diagnosis, median (IQR)	70 (64–76)
Male sex, *n* (%)	87 (100)
BM vacuoles, *n* (%)	43 (84%)
Hemoglobin (g/dL), median (IQR)	9.8 (8.4–11.4)
VEXAS phenotype	
Systemic symptoms, *n* (%)	36 (41)
Skin involvement, *n* (%)	34 (39)
Pulmonary involvement, *n* (%)	9 (10)
Hematological disease	
MGUS, *n* (%)	32 (37)
MM, *n* (%)	1 (1)
MDS, *n* (%)	49 (56)
UBA1 genotype	
p.Met41Val (c.121A>G), *n* (%)	25 (29)
p.Met41Leu (c.121A>C), *n* (%)	6 (7)
p.Met41Thr (c.122T>C), *n* (%)	35 (40)
Other, *n* (%)	21 (24)

Abbreviations: BM, bone marrow; IQR, interquartile range; MDS, myelodysplastic syndrome; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma.

Anticoagulation strategies in VEXAS

The therapeutic management of TE has seen widespread adoption of DOACs, which were also in our cohort the most commonly prescribed class of drugs (51%, $n = 22$) (Figure 3B). LMWH was used in 28% ($n = 12$) of patients, while Fondaparinux was used in 14% ($n = 6$) of cases and AVKs in 7% ($n = 3$) of patients. Analysis of hematological data revealed that the choice of LMWH was associated with a specific risk profile. Patients on LMWH therapy experienced moderate to severe thrombocytopenia (mean count 60–80 $\times 10^9$/L), which was significantly more pronounced than in patients treated with DOACs, who had a mean platelet count in the range of 120–140 $\times 10^9$/L.

Despite therapy, controlling TE proved complex, with a significant rate of recurrence. The Swimmer plot (Figure 3C) illustrates the clinical course and management of the patients with TE, highlighting how recurrent events occurred both during active anticoagulant treatment and after discontinuation thereof. Specifically, 11 out of 16 events (69%) occurred in patients who were already receiving active anticoagulant therapy, typically during disease flares or in patients who were not showing an adequate response to their VEXAS-specific treatment. A more in-depth analysis of these 16 events reveals the following distribution: $n = 8$ occurred in patients who were under DOACs, $n = 3$ in patients receiving LMWH, whereas the remaining $n = 5$ occurred after planned discontinuation of therapy. A key finding emerging from such data is the close correlation between control of VEXAS syndrome disease activity and thrombotic risk, highlighting how uncontrolled inflammation may be the main driver of thrombosis and its recurrence.

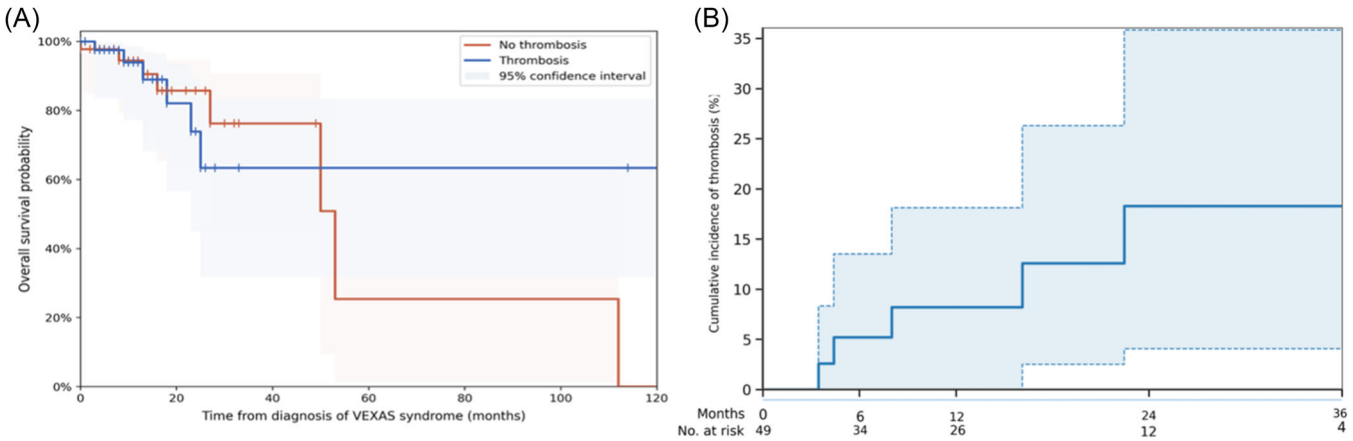

FIGURE 2 **Survival and cumulative incidence of thrombosis in patients with vacuoles, E1 enzyme, X-linked, autoinflammatory, and somatic (VEXAS) syndrome.** **(A)** Kaplan–Meier estimates of overall survival (OS) from the time of VEXAS diagnosis, stratified by the occurrence of thrombosis. Survival probabilities are displayed as step functions with shaded 95% confidence intervals (CIs). Time is expressed in months from diagnosis and log-rank is P = 0.65. **(B)** Cumulative incidence of first thrombosis after VEXAS diagnosis among patients without documented thrombosis prior to diagnosis: the incident risk set included 49 patients without prior or concomitant thrombotic events (TEs), followed from the time of molecular VEXAS diagnosis, with 5 incident TEs and death without TE as the competing event. Estimates are shown as conventional stepwise cumulative-incidence functions with shaded 95% CIs, accounting for censoring. Time is expressed in months from diagnosis.

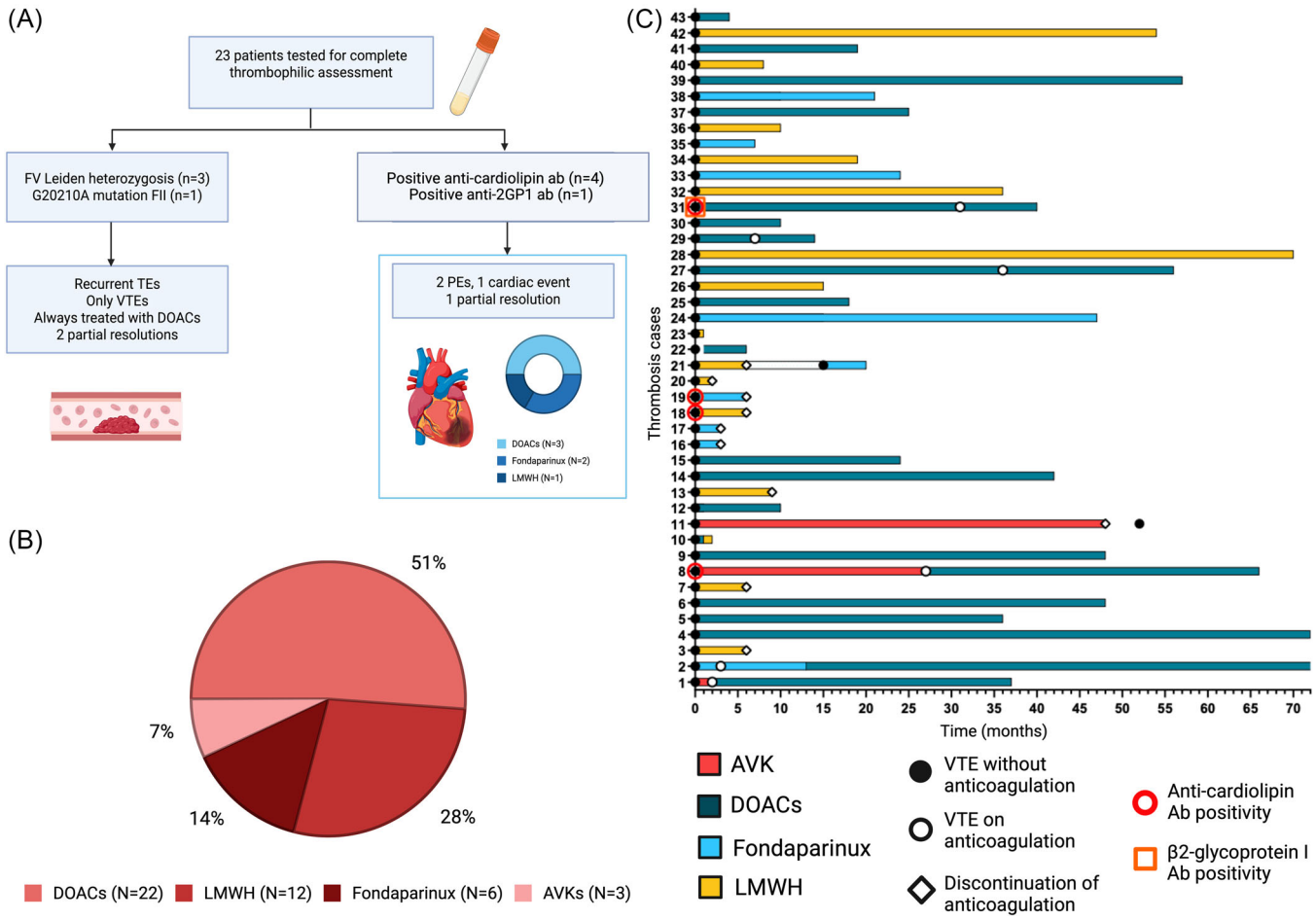

FIGURE 3 **Thrombophilic assessment and treatment of choice.** A comprehensive thrombophilic assessment was conducted in a minority of cases **(A)**, and the main results are represented in the graphic. The pie chart **(B)** displays the distribution of the preferred anticoagulant for first-line treatment of all types of thrombotic events (TE). The Swimmer plot **(C)** illustrates a detailed breakdown of the treatment strategies for venous TEs, including instances of treatment discontinuation and recurrences of TE. AVK, vitamin K antagonist; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

DISCUSSION

This national, retrospective, multicenter study represents the first systematic mapping of thrombosis associated with VEXAS syndrome in Italy, based on an analysis of 232 patient-years. The results clearly indicate that VEXAS is associated with a high risk of thrombo-inflammatory events. While the strong association between thrombosis and VEXAS has already emerged from previous retrospective studies,[6,8] each phase of our study adds its own contribution by providing novel perspectives. These include the role of a well-defined phenotype-driven *UBA1* screening in patients with unexplained thrombosis, as well as the deep characterization of TE and thrombophilic features and their role in management of VEXAS. Since part of the study consists of a retrospective multicenter cohort of identified VEXAS cases rather than a population-based incident cohort, fatal TEs occurring before VEXAS recognition, referral, or molecular diagnosis may have been underascertained. The descriptive TE-history frequency should therefore not be interpreted as a population incidence rate but rather as a vision at a glance of VEXAS-related thrombosis.

The first step of our study aimed to explore the prevalence of VEXAS syndrome in an unselected cohort of 1086 patients who had experienced TE, but none of these patients tested positive for *UBA1* mutations. This data reinforces the idea that indiscriminate use of *UBA1* testing in all patients with unexplained thrombosis is neither clinically useful nor likely sustainable. On the contrary, a more selective approach targeting individuals with a clinical picture strongly compatible with VEXAS syndrome is more rational and cost-effective, increasing the likelihood of identifying significant mutations and minimizing the emergence of broader diagnostic pathways.[15,19] In fact, our data support that testing for *UBA1* mutations should be reserved for patients with a clinical phenotype that is clearly suggestive of VEXAS syndrome and not applied systematically in all cases of idiopathic thrombosis.

The second phase of the study focused on studying TE in a national cohort of 87 patients with a confirmed diagnosis of VEXAS syndrome. In this cohort, 49% of cases had TE, a finding that confirms the association between VEXAS syndrome and a marked prothrombotic state, as already described in the literature.[4,6,10] The almost exclusive venous predominance (97% of events) further reinforces the hypothesis that the main driver of thrombosis in these patients is systemic inflammation, rather than traditional atherosclerosis, which typically underlies arterial events,[11,12] Endothelial activation, cytokine dysregulation and platelet activation, which are key elements in the pathophysiology of VEXAS syndrome, create a pro-coagulant microenvironment that manifests predominantly in the venous system, a finding which calls for parallel in other clonal

states (clonal hematopoiesis of indeterminate potential, CHIP) also characterized by increased cardiovascular and thrombotic risk.[20,21] One finding of particular clinical relevance is that in 33% of cases, the TE coincided with the onset of the disease, suggesting its role as a potential "sentinel event" of the syndrome.

The increased frequency of cases with chondritis and TE—albeit to be interpreted as an association of clinical features—is another interesting finding, possibly an expression of a particularly high inflammatory burden[22]: patients with chondritis may experience more intense endothelial activation and cytokine dysregulation, resulting in a clinical phenotype more prone to both cartilage damage and thrombosis. The high incidence of thrombosis places VEXAS syndrome among the conditions with the highest level of thrombotic risk, comparable to that of other autoimmune diseases[6] or chronic myeloid neoplasms.[23] The predominance of venous events over arterial events is consistent with other thrombo-inflammatory conditions, where activation of coagulation triggered by systemic inflammation occurs mainly in low-flow venous areas. The distinct cytokine profiles in MPNs and VEXAS differentially shape their thrombotic phenotypes: in MPNs, NLRP3-driven IL-1β and IL-18, along with erythrocytosis, hyperviscosity, and JAK2-dependent platelet activation, possibly favor arterial events.[23] Conversely, VEXAS syndrome can be classified as a clear clinical model of "thrombo-inflammation," a condition in which the activation of inflammatory pathways acts as a powerful driver of hypercoagulability.[24,25] The pathogenesis of VEXAS syndrome, triggered by somatic mutations in *UBA1*, causes a defect in the process of ubiquitination,[26] leading to an accumulation of undegraded proteins, cellular stress and mass production of pro-inflammatory cytokines.[27] This inflammatory "milieu" in turn promotes a prothrombotic state through platelet activation, endothelial damage and increased coagulation factors, ultimately generating a more venous-predominant thrombosis.[8] The fact that one-third of TE occur at the onset of the disease, whereas others occur during flares strongly suggests that uncontrolled systemic inflammation, typical of the initial phases or flares of VEXAS, may act as a powerful trigger, as previously suggested.[8] This mechanism bears strong similarities to other chronic inflammatory diseases, such as Behçet syndrome or inflammatory bowel disease (IBD), in which it is well known that phases of disease activity are associated with a significant increase in thrombotic risk.[28-30] Such marked activation of the innate immune system may also be linked to an imbalance of NET–complement–immunothrombosis axis. NETs may contribute by providing a scaffold of DNA and histones for clot assembly, exposing tissue factor and cationic proteins that activate coagulation, and stimulating endothelial cells and monocytes, thereby perpetuating a vicious cycle of inflammation and thrombosis, amplified by complement activation.[6,31]

The management of thrombosis in patients with VEXAS syndrome is complex, and there are no specific guidelines. In our cohort, most patients with VTE were treated with DOACs. However, recent scientific literature has raised doubts about the efficacy of DOACs, in particular for conditions such as antiphospholipid syndrome (APS), especially in triple-positive patients or those with a history of arterial thrombosis.[32] Several international scientific societies recommend caution or advise against the use of DOACs in all patients with APS, preferring AVKs for first-line therapy.[33] Although patients with VEXAS syndrome are typically negative for aCL and anti-β_2GPI,[7] chronic systemic hyperinflammation could represent another "high-intensity" prothrombotic condition in which the efficacy of DOACs may be suboptimal compared to AVKs, especially if associated with antibody positivity as in some of our cases. A valuable option could be to monitor the antibody titers over time, as there have been instances of seroreversions occurring even after obtaining relatively high titers, thereby considering a switch to AVK for those maintaining elevated titers over time. One could hypothesize that systemic inflammation, VEXAS disease status (active flare vs. controlled disease), and concomitant clinical conditions (e.g., infectious episodes) may all influence antiphospholipid antibody patterns.

The high rate of TE recurrence, with 16 events in addition to the primary ones, outlines a phenotype of persistent and severe thrombotic risk. The most critical observation is that almost 70% of such events (11 out of 16) occurred in patients already under anticoagulant therapy. Endothelial and platelet activation sustained by inflammatory cytokines likely creates such an intense stimulus that standard anticoagulants are insufficient to prevent its consequences. These data challenge the adequacy of a time-limited anticoagulant approach in this disease. Given the chronic and recurrent nature of the underlying inflammation in VEXAS syndrome, it is plausible that the thrombotic risk remains elevated over time. This suggests the need to consider long-term, if not indefinite, anticoagulant therapy after an initial TE, especially in patients who do not achieve complete and stable control of their inflammatory disease or carry inherited or acquired thrombophilia.

In conclusion, our study confirms that VEXAS syndrome is a condition associated with a very high risk of thrombosis, with almost half of patients experiencing TE, mainly venous in nature, during their clinical history. Thrombosis often presents as one of the initial manifestations, highlighting the inextricable link between systemic inflammation driven by the *UBA1* mutation and the activation of the coagulation cascade.[24,28] Screening for VEXAS syndrome should not be performed routinely in patients with idiopathic thrombosis, being targeted to cases with a strong clinical suspicion, based on the coexistence of typical hematological and rheumatological manifestations. In light of these findings, it is imperative that clinicians maintain a high level of suspicion for thromboembolic complications in patients with VEXAS syndrome, both at diagnosis and during follow-up. It is reasonable to consider long-term anticoagulant therapy for patients with VEXAS syndrome who develop TE, given the chronic and recurrent nature of the underlying condition. Choosing the best anticoagulant (DOACs vs. AVKs) remains an area of uncertainty, and a personalized approach should be taken, balancing the thrombotic risk with the hemorrhagic risk of the individual patient in light of comprehensive baseline thrombophilia testing, pending more robust prospective data. Prospectively exploring the efficacy and safety of different anticoagulation strategies (DOACs vs. AVKs) in this specific patient population is a clinical unmet need. A thorough baseline thrombophilic assessment is warranted also to assist clinicians in determining whether the addition of prophylactic anticoagulation might be appropriate, particularly during disease flares. Finally, translational studies may help elucidate the specific molecular mechanisms linking *UBA1* dysfunction to hypercoagulability, potentially paving the way for targeted therapies capable of simultaneously controlling both the inflammatory and thrombotic components of VEXAS syndrome.

AUTHOR CONTRIBUTIONS

Giorgia Ranucci: Writing—original draft; data curation. **Maria Rosaria Pascale**: Writing—original draft; data curation. **Vittorio Forte**: Validation. **Elisa Diral**: Validation. **Corrado Campochiaro**: Validation. **Jacqueline Ferrari**: Validation. **Mariachiara Cuccaro**: Validation. **Chiara Cattaneo**: Validation. **Francesca Crisafulli**: Validation. **Lucia Cardillo**: Validation. **Valeria Renola**: Validation. **Elisa Meddi**: Validation. **Marianna Velocci**: Validation. **Elisa Casciani**: Validation. **Francesca Romano**: Validation. **Pellegrino Musto**: Validation. **Serafina Barbato**: Validation. **Giorgia Battipaglia**: Validation. **Marco Frigeni**: Validation. **Erika Morsia**: Validation. **Arianna Savi**: Validation. **Cristina Papayannidis**: Validation. **Elena Crisà**: Validation. **Laura Cicconi**: Validation. **Isabella Capodanno**: Validation. **Alfonso Fiumarella**:

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data and results of the survey from which results were generated are available in the manuscript. Additional request can be directed via email to the corresponding author.

ETHICS STATEMENT

Review and collection of clinical and molecular data were performed in accordance with the protocols and written consent approved by the institutional review boards of each participating institution and guidelines set forth by the Declaration of Helsinki.

FUNDING

This work was also supported by AIRC 5 × 1000 call "Metastatic disease: The key unmet need in oncology" to MYNERVA project, #21267 (Myeloid Neoplasms Research Venture AIRC. A detailed description of the MYNERVA project is available at http://www.progettoagimm.it). This work was also supported by MUR-PNRR M4C2I1.3 PE6 project PE00000019 Heal Italia, PRIN grant 2017WXR7ZT, Ministero della Salute, Rome, Italy (Finalizzata 2018, NET-2018-12365935; personalized medicine program on myeloid neoplasms: characterization of the patient's genome for clinical decision making and systematic collection of real-world data to improve quality of health care) (M.T.V.).

SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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