Journal of Thrombosis and Thrombolysis
https://doi.org/10.1007/s11239-025-03238-4

Prospective evidence of increased venous thromboembolism in hereditary hemorrhagic telangiectasia

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Received: 11 September 2025 / Accepted: 30 December 2025

Abstract

Hereditary Hemorrhagic Telangiectasia (HHT) is a rare vascular disease (1/5,000 prevalence) characterized by mucocutaneous telangiectasias and visceral arteriovenous malformations. Although hemorrhagic manifestations predominate, patients may also be at increased risk of thrombotic events. Previous studies on this topic have been mostly retrospective, and prospective data are lacking. We conducted a prospective registry-based study using a validated adjudication system to assess the incidence of venous thromboembolism (VTE) in subjects with a definite diagnosis of HHT. A total of 315 patients were included (mean age 54.3 ± 17.8 years; median 57, IQR 18–93; 42.2% > 65 years; 172 men, 143 women). Median follow-up was 14 months (IQR 6–99). Fifteen VTE events occurred, yielding an overall incidence of 23.1/1,000 patient-years. Incidence was 45.1/1,000 patient-years in subjects > 65 years-old and 11.6/1,000 patient-years in those ≤ 65 years-old. Four events were unprovoked, and eleven had identifiable provoking factors. In 4 cases, the provoking factor was hospitalization for an acute disease or the exacerbation of a chronic condition; none of these patients received in-hospital thromboprophylaxis. The observed VTE incidence in HHT appears higher than in the general population, particularly among older individuals. Underuse of prophylaxis may contribute to this excess risk. These findings underscore the need for individualized strategies that balance hemorrhagic and thrombotic complications in HHT.

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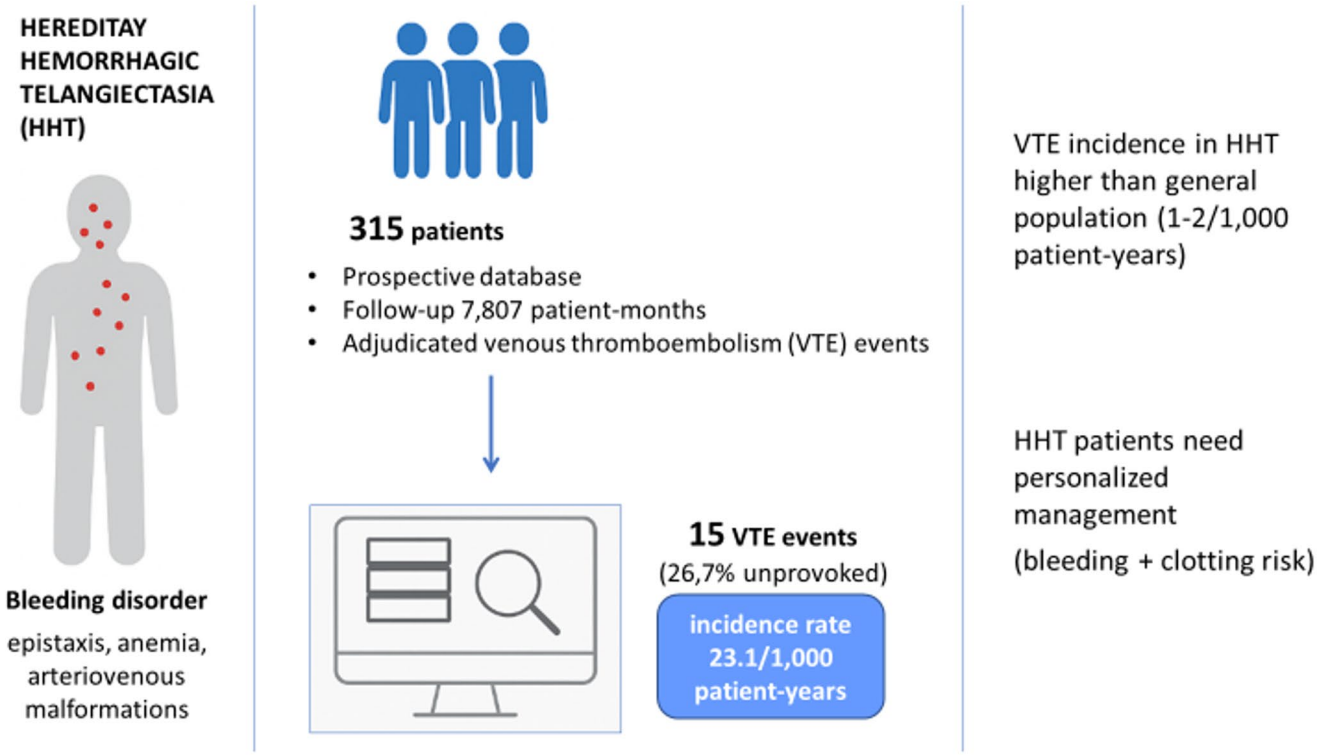
Published online: 06 March 2026

Graphical abstract



Keywords Hereditary hemorrhagic telangiectasia · Venous thromboembolism · Personalized medicine

Introduction

Hereditary Hemorrhagic Telangiectasia (HHT) is a rare autosomal dominant vascular disease with an estimated prevalence of approximately 1/5,000–8,000 individuals. It is characterized by mucocutaneous telangiectasias and visceral arteriovenous malformations (AVMs), most commonly affecting the lungs, liver, brain, and gastrointestinal tract [1, 2].

Although HHT is primarily associated with hemorrhagic manifestations, several studies have suggested that patients may also be at increased risk of thrombotic events. In a cohort of 309 patients, Shovlin et al. reported 20 venous thromboembolic (VTE) events, corresponding to a prevalence of 6.5% [3]. A subsequent larger series by Livesey et al., which included this same cohort along with additional patients (total ≈ 600), found a VTE incidence rate of 138.3 per 100,000 patient-years—higher than that observed among hospitalized patients in the general population [4]. In contrast, a Norwegian study by Jørgensen et al. found a VTE prevalence of 23.1% among 134 patients [5], while a Danish nationwide case-control study by Aagaard et al. reported no difference in VTE incidence between 73 patients with HHT and 219 matched controls over 20 years of follow-up [6]. The mechanisms underlying a potential prothrombotic tendency in HHT remain uncertain. Chronic iron-deficiency anemia, leading to elevated plasma levels of coagulation factor VIII, has been proposed as a major contributor [3–6].

To address this knowledge gap, we evaluated the incidence of VTE in patients with HHT using a prospectively maintained registry with systematic, adjudicated confirmation of thrombotic events.

Methods

Study setting and patient population

The study was conducted at a tertiary referral center for Hereditary Hemorrhagic Telangiectasia (HHT), active since 2016. The center receives nationwide referrals for the evaluation of suspected or confirmed HHT, typically prompted by epistaxis, gastrointestinal bleeding, evidence of visceral arteriovenous malformations (AVMs), or a family history of the disease. Relatives of index cases are invited for screening regardless of symptom severity, and the center collaborates closely with the Italian HHT patient association (HHT

Onlus). As of October 2025, more than 400 patients with confirmed HHT are followed in the center's registry.

Registry and data collection

Clinical information is systematically recorded in a prospectively maintained electronic registry, continuously updated by dedicated staff. Data include demographics, comorbidities, clinical manifestations, therapies, laboratory and imaging findings, hospitalizations, emergency department visits, and procedures. All patients provide written informed consent and are instructed to notify the center of hospitalizations, new diagnoses, or therapy changes.

Study design and follow-up

This was a prospective, registry-based cohort study approved by the local ethics committee (protocol 6241/20, ID 2999, February 20, 2020). Consecutive adult patients (≥ 18 years) with a definite diagnosis of HHT—either genetically confirmed or fulfilling Curaçao clinical criteria [2]—and at least 6 months of prospective follow-up were included. Exclusion criteria were: (i) uncertain HHT diagnosis; (ii) < 6 months of follow-up; (iii) incomplete clinical or follow-up information precluding reliable outcome assessment; and (iv) ongoing anticoagulation at the time of referral. Follow-up continued until the last clinical contact, a VTE event, loss to follow-up, or study censoring (December 31, 2023), whichever occurred first. Patients lost to follow-up were censored at their last available contact.

VTE event ascertainment

Incident venous thromboembolism (VTE) was defined as any of the following: (i) symptomatic or incidental deep vein thrombosis (DVT) of the lower or upper limbs; (ii) symptomatic or incidental pulmonary embolism (PE; at least segmental or ≥2 subsegmental branches); or (iii) symptomatic or incidental splanchnic vein thrombosis. Events were identified through scheduled follow-up visits, structured telephone interviews, and review of external medical documentation, including imaging reports and discharge summaries. No event was recorded solely based on patient self-report. All events were adjudicated by at least two independent reviewers according to predefined diagnostic criteria; disagreements were resolved by consensus. For each VTE event, available records were reviewed for potential provoking factors (e.g., surgery, hospitalization, immobilization, cancer, infection, thrombophilia, pregnancy, prolonged travel, oral contraceptive use, or prothrombotic medications). Events without identifiable risk factors were classified as unprovoked. Data on therapies potentially affecting thrombotic risk, including bevacizumab and tranexamic acid, were extracted from the registry and analyzed in relation to incident VTE events.

Statistical analyses

Descriptive statistics were used to summarize the demographic and clinical characteristics of the patients. The results are expressed as mean ± SD, or median (IQR), or as a percentage. Differences between groups were compared by Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. The incidence rate for thromboembolic events in the total follow-up time was calculated and expressed as the number of events per 1,000 patient-years and was also stratified by age. SPSS 20.0 software was used to perform the statistical analysis.

Results

A total of 315 patients with definite HHT were included in the analysis. The mean age was 54.3 ± 17.8 years, and the median age was 57 years (interquartile range [IQR], 18–93). Overall, 133 patients (42.2%) were older than 65 years. There were 172 men and 143 women. Epistaxis and chronic iron deficiency anemia were present in 97.8% and 51.1% of patients, respectively. Most patients (98.1%) belonged to a definite HHT family. Genetic tests were available for 237 patients: pathogenic variants of *ENG* gene were found in 79 patients (HHT1), while pathogenic mutations of *ACVRL1* gene were present in 158 patients (HHT2). Regarding vascular malformations, pulmonary AVMs were found in 42.5% of patients, hepatic AVMs were found in 49.5% of patients and cerebrovascular malformations were present in 8.9% of patients. Previous gastrointestinal bleeding was documented in 67 patients (21.3%). The demographic and clinical baseline characteristics of the overall cohort, as well as of patients who developed VTE compared with those who did not, are summarized in Table 1. Among patients with incident VTE, the mean age was 63.9 ± 14.3 years, and the median age was 66 years (IQR, 32–82); 10 of 15 (66.7%) were older than 65 years. Age was significantly higher in the VTE group than in the non-VTE group ($p = 0.02$). In addition, patients with incident VTE had a significantly higher prevalence of cancer at baseline ($p = 0.01$).

Information regarding the follow-up time and the incident VTE events are reported in Table 2. All patients had at least 6 months of follow-up. The median follow-up was 14 months (IQR, 6–99), corresponding to a total of 7,807 patient-months. Figure 1 shows the distribution of individual follow-up times.

Table 1 Demographic and clinical characteristics of the study population

Characteristics	Whole cohort ($n=315$)	VTE group ($n=15$)	Non-VTE group ($n=300$)	p-value
Mean age, years ± SD	54.3 ± 17.8	63.9 ± 14.3	53.8 ± 17.8	0.02
Median age, years (IQR)	57 (18–93)	66 (32–82)	55 (18–93)	
> 65 years-old, n (%)	133 (42.2%)	10 (66.7%)	123 (41.0%)	
Males/Females	172/143	8/7	164/136	n.s.
Epistaxis, n (%)	308 (97.8%)	15 (100%)	293 (97.7%)	n.s.
Family history of HHT, n (%)	309 (98.1%)	15 (100%)	294 (98.0%)	n.s.
Mucocutaneous telangiectases, n (%)	286 (90.8%)	13 (86.7%)	273 (91.0%)	n.s.
Chronic iron deficiency anemia, n (%)	161 (51.1%)	9 (60.0%)	152 (50.7%)	n.s.
HHT1/HHT2/Clinical diagnosis	79/158/78	5/8/2	74/150/76	n.s.
Pulmonary AVMs, n (%)	134 (42.5%)	5 (33.3%)	129 (43.0%)	n.s.
Hepatic AVMs, n (%)	156 (49.5%)	9 (60.0%)	147 (49.0%)	n.s.
Cerebral vascular malformations, n (%)	28 (8.9%)	1 (6.7%)	27 (9.0%)	n.s.
Previous gastrointestinal bleeding, n (%)	67 (21.3%)	4 (26.7%)	63 (21.0%)	n.s.
Comorbidities, n (%)				
- Hypertension	48 (15.2%)	4 (26.7%)	44 (14.7%)	n.s.
- Diabetes mellitus type 2	23 (7.3%)	2 (13.3%)	21 (7.0%)	n.s.
- Coronary artery disease	4 (1.3%)	0 (0.0%)	4 (1.3%)	n.s.
- Chronic heart failure	39 (12.4%)	1 (6.7%)	38 (12.7%)	n.s.
- Chronic kidney disease	26 (8.2%)	1 (6.7%)	25 (8.3%)	n.s.
- Chronic obstructive pulmonary disease	27 (8.6%)	0 (0.0%)	27 (9.0%)	n.s.
- Liver cirrhosis	6 (1.9%)	0 (0.0%)	6 (20.0%)	n.s.
- Cancer	12 (3.8%)	3 (20%)	9 (3.0%)	0.015
- Previous venous thromboembolism	7 (2.2%)	1 (6.7%)	6 (2.0%)	n.s.

SD: standard deviation; n: number; HHT1: Hereditary Hemorrhagic Telangiectasia 1; HHT2: Hereditary Hemorrhagic Telangiectasia 2; AVMs: arteriovenous malformations; IQR: interquartile range; n.s: not significant

Table 2 Incident VTE events

Total follow-up time, months	7,807
Median follow-up, months (IQR)	14 (6–99)
VTE, n	15
- Lower leg DVT, n	5
- Upper limb DVT, n	1
- PE, n	4
- DVT + PE, n	2
- Splanchnic vein thrombosis, n	3
Incidence of VTE in the whole cohort	23.1 per 1,000 pt/years
Incidence of VTE in patients > 65 years-old	45.1 per 1,000 pt/years
Incidence of VTE in patients ≤ 65 years-old	11.6 per 1,000 pt/years

SD: standard deviation; VTE: venous thromboembolism; DVT: deep venous thrombosis; PE: pulmonary embolism

During follow-up, 15 VTE occurred. In detail, 5 patients developed DVT of the lower limbs, 1 patient developed DVT of the upper limb, 4 patients had PE, 2 patients had DVT and PE, and 3 patients had a splanchnic vein thrombosis. Of the 15 VTE events, 12 were symptomatic, and 3 were incidentally detected on imaging performed for unrelated indications. All incidental events met diagnostic criteria and were included in the incidence calculations. The overall incidence rate of VTE was 23.1/1,000 patient-years. Incidence was 45.1/1,000 patient-years in subjects > 65 years-old and 11.6/1,000 patient-years in subjects ≤ 65 years-old, respectively.

Table 3 provides information on the 15 incident VTE events. There were 4 unprovoked events (26.7%): 2 PE, 1 lower limb DVT with PE, and 1 splanchnic vein thrombosis, occurring after 8–42 months of follow-up. The remaining 11 events (73.3%) were associated with increased VTE risk factors: cancer (3 cases), hospitalization for an acute disease (3 cases) or exacerbation of a chronic disease (1 case), acute infection or inflammation (2 cases), bone fracture (1 case), and antiphospholipid syndrome (1 case, diagnosed retrospectively after the event). Of the 15 patients, only 1 had a previous thrombotic event (a patient with pancreatic cancer and prior PE); all others experienced their first episode. The time from study entry to the VTE event ranged from 1 to 78 months (median 12 months, IQR 8–42). Notably, none of the 4 patients who developed VTE during hospitalization had received thromboprophylaxis. The patient with pancreatic cancer and prior PE was not receiving secondary prevention. The 2 other patients with cancer, the patient with bone fracture, and the patient with APS were also not receiving thromboprophylaxis before the event. Finally, 2 patients (one with a previous stroke and one with Horton's disease) were on antiplatelet therapy at the time of VTE. During follow-up, 1 patient received treatment with bevacizumab and 23 patients reported occasional use of tranexamic acid during bleeding episodes. None of the VTE events occurred in patients treated with bevacizumab or tranexamic acid.

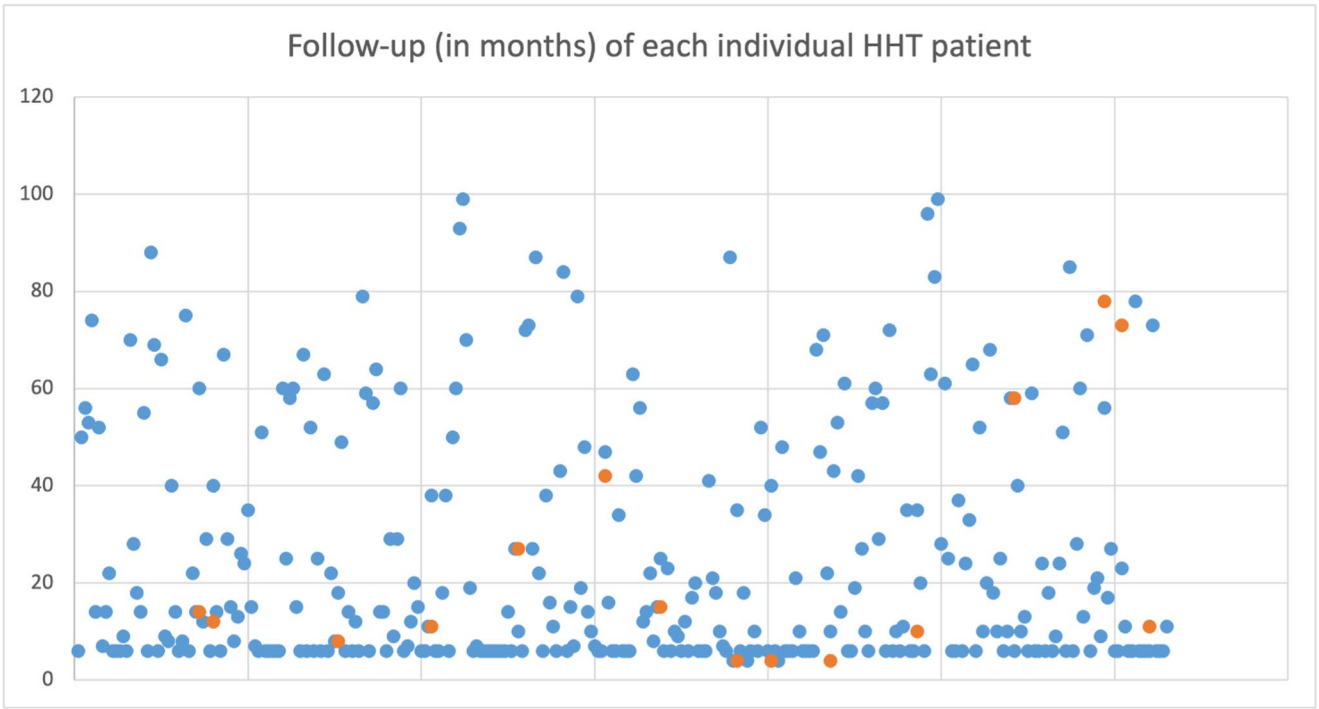


Fig. 1 Graphical representation of follow-up duration (in months) of each patient included in the analysis. Red circles represent patients who developed VTE

Table 3 Type of VTE events

Incident VTE event	Concomitant conditions of increased risk of VTE	Follow-up (in months) before the incident VTE event
PE (incidental)	None (unprovoked event)	10
PE (symptomatic)	Hospitalization for brain abscess / no thromboprophylaxis during hospitalization	11
PE (incidental)	None (unprovoked event)	42
PE (symptomatic)	SARS-CoV-2 infection	78
DVT of the legs (symptomatic)	Femoral bone fracture	1
DVT of the legs (symptomatic)	Hospitalization for acute anemia / no thromboprophylaxis during hospitalization	4
DVT of the legs (symptomatic)	Exacerbation of Horton's disease	11
DVT of the legs (symptomatic)	Hospitalization for ischemic stroke / no thromboprophylaxis during hospitalization	14
DVT of the legs (symptomatic)	Hospitalization for decompensated heart failure / no thromboprophylaxis during hospitalization	15
DVT of the legs + PE (symptomatic)	Renal cell adenocarcinoma	2
DVT of the legs + PE (symptomatic)	None (unprovoked event)	8
DVT of the upper limb (symptomatic)	Breast cancer	58
Splanchnic vein thrombosis (symptomatic)	None (unprovoked event)	12
Splanchnic vein thrombosis (incidental)	APS	27
Splanchnic vein thrombosis (symptomatic)	Pancreatic cancer / previous VTE / no secondary VTE prevention	73

VTE: venous thromboembolism; PE: pulmonary embolism; DVT: deep venous thrombosis; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; APS: antiphospholipid syndrome

Discussion

This prospective registry-based study evaluated the incidence of VTE in patients with HHT using adjudicated outcomes. Among more than 300 patients, we observed an incidence rate of 23.1 per 1,000 patient-years, rising to 45.1 per 1,000 patient-years in individuals aged > 65 years. These rates are markedly higher than the 1–2 per 1,000 person-years reported in the general European population [7] and exceed the expected 6–8 per 1,000 person-years for adults aged 65 years and older [8, 9], underscoring that VTE is an underrecognized complication in HHT.

Our results align with previous retrospective studies suggesting increased thrombotic risk [3–5], though they contrast with the Danish case–control study that found no excess events [6]. The prospective registry design, systematic event adjudication, and verification with medical records minimize the risk of underreporting and strengthen the validity of our findings.

The mechanisms remain uncertain. Chronic iron deficiency anemia, leading to elevated factor VIII, is the most widely proposed explanation [3–6], but endothelial dysfunction or systemic inflammation may also contribute. Notably, more than one-quarter of VTE events were unprovoked, supporting the hypothesis of disease-related prothrombotic mechanisms. In our cohort, patients who developed VTE were significantly older and had a higher prevalence of cancer compared with those without VTE, consistent with well-established risk factors that may further amplify thrombotic susceptibility in HHT.

Analysis of provoking factors highlighted missed opportunities for prophylaxis. None of the four patients who developed VTE during hospitalization had received thromboprophylaxis, and a patient with pancreatic cancer and prior PE was not on secondary prevention. In contrast, other events occurred in settings where guideline-based prophylaxis was not formally indicated (e.g., ambulatory cancer patients with low Khorana score, acute bone fracture, or retrospectively diagnosed APS). These observations likely reflect a combination of therapeutic caution due to perceived bleeding risk and gaps in adherence to prophylactic recommendations. Reluctance likely stems from the perception of HHT patients as exclusively bleeding-prone. This is particularly important if one considers that patients with HHT often require hospitalization. In our cohort of 315 HHT patients, there were 154 hospitalizations during follow-up. Of these, 58 were due to emergency situations and 96 were planned hospitalizations for the execution of diagnostic and/or therapeutic procedures. Failing to use prophylaxis when indicated may contribute to the thrombotic burden in HHT, underscoring the importance of individualized risk–benefit assessment.

While some patients in our cohort received therapies potentially affecting thrombotic risk, all VTE events occurred in individuals not exposed to these agents, suggesting that the observed incidence is primarily related to HHT itself, the characteristics of the patients, or the management patterns during hospitalization.

Limitations of our study include the single center design, absence of a control group, and median follow-up shorter than the maximum observation period. We did not have access to a regional or national database to confirm capture of all VTE events. However, the nationwide referral nature of our center, structured follow-up, and cumulative observation exceeding 7,800 patient-months likely ensured identification of most events. Missed events would, if anything, underestimate rather than overestimate the true incidence. Additional potential biases include modest male predominance, a higher prevalence of pulmonary AVMs, older age, and chronic iron deficiency anemia—all factors that may increase VTE risk and reflect referral of more severely affected patients. We also did not retrospectively collect data on hospitalizations occurring in the year prior to study inclusion, and therefore cannot determine whether patients were hospitalized during that period. However, the four unprovoked VTE events occurred after 8, 10, 12, and 42 months of prospective follow-up, making a temporal link with prior hospitalization unlikely.

In conclusion, HHT patients appear to face a higher risk of VTE than the general population. Recognition of this thrombotic component is essential for personalized care in a disease classically defined by bleeding. Future strategies should integrate both hemorrhagic and thrombotic risks to guide comprehensive management.

Author contributions Eleonora Gaetani: Conceptualization, Methodology, Data curation, Formal analysis, Writing – review & editing. Luigi Di Martino: Data collection, Investigation, Statistical analysis, Resources, Writing – review & editing. Fabiana Agostini: Validation, Visualization, Writing – review & editing. Daniela Feliciani: Patient recruitment, Clinical assessment, Data acquisition. Barbara Funaro: Patient recruitment, Clinical assessment, Data acquisition. Annarita Barberio: Patient recruitment, Clinical assessment, Data acquisition. Antonio Gasbarrini: Supervision, Project administration, Writing – review & editing. Roberto Pola: Conceptualization, Supervision, Methodology, Writing – review & editing. All authors read and approved the final manuscript.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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