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ORIGINAL ARTICLE

Long-term outcomes of patients with cerebral vein thrombosis: a multicenter study

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Summary. *Background:* Little information is available on the long-term clinical outcome of cerebral vein thrombosis (CVT). *Objectives and methods:* In an international, retrospective cohort study, we assessed the long-term rates of mortality, residual disability and recurrent venous thromboembolism (VTE) in a cohort of patients with a first CVT episode. *Results:* Seven hundred and six patients (73.7% females) with CVT were included. Patients were followed for a total of 3171 patient-years. Median follow-up was 40 months (range 6, 297 months). At the end of follow-up, 20 patients had died (2.8%). The outcome was generally good: 89.1% of patients had a complete recovery (modified Rankin Score [mRS] 0–1) and 3.8% had a partial recovery and were independent (mRS 2). Eighty-four per cent of patients were treated with oral anticoagulants and the mean treatment duration was 12 months. CVT recurred in 31 patients (4.4%), and 46 patients (6.5%) had a VTE in a different site, for an overall incidence of recurrence of 23.6 events per 1000 patient-years (95% confidence Interval [CI] 17.8, 28.7) and of 35.1 events/1000 patient-years (95% CI, 27.7, 44.4) after anticoagulant therapy withdrawal. A previous VTE was the only significant predictor of recurrence at multivariate analysis (hazard ratio [HR] 2.70; 95% CI 1.25, 5.83). *Conclusions:* The long-term risk of mortality and recurrent VTE appears to be low in patients who survived the acute phase of CVT. A previous VTE history independently predicts recurrent events.

Keywords: anticoagulant treatment, cerebral vein thrombosis, mortality, recurrence.

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Introduction

Cerebral vein thrombosis (CVT) has long been considered a rare disease with important long-term morbidity and mortality rates [1,2]. In the last decade, new non-invasive diagnostic techniques have increased the frequency with which this disease is diagnosed and there has been increasing evidence that an early diagnosis and a timely start of anticoagulant treatment significantly reduced morbidity from CVT and improved survival [3].

Recent guidelines recommend the use of unfractionated heparin or low-molecular-weight heparin followed by at least 3–6 months of oral anticoagulant therapy (OAT) with vitamin K antagonists for most patients with a first episode of CVT [4,5]. However, the optimal duration of anticoagulant treatment is not established because little information is available on the long-term rate of recurrent CVT or the rate of recurrence of venous thromboembolic events (VTE) in other sites after the discontinuation of anticoagulant drugs. These rates have been reported to be low in a large prospective study [6], and these findings were confirmed by a subsequent meta-analysis that included 19 studies for a total of about 1500 patients [7]. However, these results were based on relatively short periods of follow-up. Furthermore, almost all published studies were too small to evaluate potential risk factors for recurrence. More recently, a large cohort study from a single center confirmed the

substantially low rate of recurrences after a longer-term follow-up [8].

Thus, to better estimate the long-term recurrence rates of CVT and to accurately identify risk factors for recurrence, we conducted a large, international, multicenter, retrospective cohort study in a population of patients with a first episode of CVT.

Methods

The study involved 27 centers from Italy, Czech Republic and the USA. The complete list of participating centers is available in Appendix 1.

All centers were Thrombosis Units, Anticoagulation Clinics or Neurology Clinics. These centers are routinely involved in the management of CVT patients from the time of diagnosis and the start of anticoagulant treatment or are subsequently involved in the monitoring of OAT and the evaluation of specific risk factors, such as thrombophilia, after the first days of acute treatment. All involved centers regularly perform long-term follow-up of these patients.

At each participating center, data on consecutive cases of patients with a first episode of objectively diagnosed CVT were collected. All eligible patients have been regularly followed by the local anticoagulation clinics and/or by neurology clinics/stroke units. As the main aim of the study was to evaluate the clinical history of CVT, only patients with an available follow-up of at least 6 months or with an outcome event occurring within the first 6 months (death, recurrence of CVT and occurrence of VTE) were included in the study. However, to explore the presence of potential differences in the population with and without follow-up, their baseline characteristics were compared.

Case report forms were prepared by the coordinating center (Varese, Italy) and were sent to all participating centers. Local investigators were asked to fill out the form and to send it back to the coordinating center. All data were cross-checked and validated centrally at the end of the follow-up period.

Demographic data, site of thrombosis, medical history focusing on potential risk factors for thrombosis, treatment and clinical outcome were gathered. Furthermore, information on family and a personal history of VTE was also collected. A positive personal history of VTE was adjudicated if the patient had a previous objectively assessed episode of a deep vein thrombosis, pulmonary embolism, splanchnic vein thrombosis or CVT. A positive family history of VTE was adjudicated when one or more first-degree relatives had an objectively assessed episode of VTE.

Cerebral vein thrombosis was defined as secondary in the presence of one of the following risk factors: cancer, infections, trauma, oral contraceptive (OC) use, pregnancy, puerperium, hormone replacement therapy (HRT), neurosurgery and myeloproliferative neoplasms. In the absence of the aforementioned predisposing factors, the CVT episode was defined as unprovoked. Information on thrombophilic abnormalities, including antithrombin, proteins C and S, factor V Leiden, and G20210A mutations, homocysteine, lupus anticoagulant, anticardiolipin antibodies, antibeta2glycoprotein I antibodies were collected when available.

Information on clinical events during follow-up was first collected using the computerized database of each anticoagulation clinic or neurology department, where data on patients' outcomes are regularly collected. Furthermore, for the purpose of this study and in order to guarantee the most accurate and updated information, investigators were requested to contact all included patients by means of a visit at the center, a telephone contact, or a mailed questionnaire if this was not scheduled during their regular clinical activity. At the time of contact, information on CVT recurrence, on the occurrence of VTE in other sites, and on the death of the patient was collected and was added to the information stored at each center database. For all reported events, accurate evaluation of source documentation was requested. Only objectively diagnosed events were considered. Accepted tests were the following: magnetic resonance (MR) imaging with MR venography, computed tomography (CT) venography, or conventional angiography for the diagnosis of recurrent CVT; compressive B-mode ultrasound or echo-color Doppler for the diagnosis of lower or upper extremity deep vein thrombosis; perfusion or ventilation/perfusion lung scan or helical-computed tomography for the diagnosis of pulmonary embolism. Adjudication of CVT recurrence after objective testing was performed locally at each participating center.

Finally, information on the cause of death was requested. The following data were also recorded for this study: the presence of residual disability at the time of the last patient contact (defined according to the modified Rankin Scale [mRS]) [9] and current and previous antithrombotic treatments. Residual disability was classified according to the mRS as complete recovery (mRS 0–1); partial recovery, independent (mRS 2); dependent (mRS 3–5); and death (mRS 6).

The Institutional Review Board approved the study, which was carried out and is reported according to the Strengthening the Reporting of observational Studies in Epidemiology (STROBE) guidelines for observational studies [10].

Continuous variables were expressed as mean plus or minus the standard deviation (SD) or as median with minimum and maximum values when data did not have a normal distribution; categorical data are given as counts and percentages. The annual incidence of recurrent thrombosis was calculated for the whole group of venous thromboses and then separately for CVT and VTE in other sites by dividing the number of events by the total number of patient-years followed until the VTE or death. To explore the potential role of anticoagulant therapy on the risk of recurrent thrombosis, separate data of the risk of recurrence during anticoagulation and after anticoagulation discontinuation were provided. The 95% confidence intervals (CIs) were based on the exact approximation of the Poisson distribution. Because of the low recurrence rates of VTE, when the analysis was limited to specific subgroups, only crude estimates of the incidence were given. Recurrence-free survival was calculated using the Kaplan–Meier method [11]. The role

of potential risk factors for thrombosis recurrence was evaluated using the Cox proportional-hazard model [12]. All the potential risk factors for VTE were introduced in the Cox model. The impact of different severities of thrombophilia was analyzed.

Severe thrombophilia was defined as the presence of antithrombin, protein C or protein S deficiency, antiphospholipid antibodies and by the concomitant presence of more than one abnormality [13]. As a first step, the risk of thrombosis recurrence in patients with thrombophilia was compared with that of patients without thrombophilia. Subsequently, the risk of thrombosis recurrence in patients with severe thrombophilia was compared with that of patients without severe thrombophilia. We first gave unadjusted hazard ratios (HRs) estimates and then we adjusted the estimates for other possible confounders. A *P*-valued of < 0.05 was chosen as the cut off for statistical significance. All statistical analyzes were performed with SPSS 11.0 for Windows.

Results

Seven hundred and 41 patients with a first episode of CVT were considered for inclusion during the study period. For 35 patients (4.9%) the duration of follow-up was insufficient ($<$ 6 months) and these patients were excluded from the analysis. Baseline characteristics of patients with and without a sufficient follow-up were not different (data not shown). Hence, 706 patients (mean age 40.0 $\pm$ 16.3 years) were included in the study. Baseline demographic and clinical characteristics, and potential risk factors for CVT are listed in Table 1.

Four hundred and two patients (55.8%) had at least one risk factor, whereas in 304 patients (44.2%) CVT was idiopathic. Significantly more women had at least one risk factor compared with men (61.0% vs. 45.7%; $P < 0.05$). As not all thrombophilic abnormalities were tested in all of the patients, we provided separate results for each thrombophilic abnormality (see the Appendix Table A1).

The median duration of anticoagulant treatment was 12 months and 134 patients (19.0%) were still on OAT at the time of the last contact. The median duration of follow-up was 40 months (range 1–297 months) for a total follow-up of 3171 patient-years. Total follow-up during anticoagulation was 1143 patient-years and after anticoagulation discontinuation was 2028 patient-years.

The outcome of these patients was generally good: 89.1% of patients had a complete recovery (mRS 0–1) and 3.8% had a partial recovery and were independent (mRS 2). Over the time period of this study, there were 20 deaths in patients with CVT for a mortality rate of 2.8%. The cause of death was most commonly malignancy related ($n = 12$). Other causes included consequences of CVT ($n = 2$), arterial stroke ($n = 2$), fatal arrhythmia ($n = 1$), hepatic failure ($n = 1$) and sepsis ($n = 1$). In one patient the cause of death was unknown. Three deaths occurred within 1 month. Patients with a concomitant intracranial hemorrhage at presentation had a slightly, but not significant worse prognosis (mRS $\geq$ 3) at the end of follow-up in comparison with patients without concomitant intracranial hemorrhage at presentation (9.1% vs. 7.1%; *P* 0.42). The estimated survival was 98% at 1 year and 95% at 5 years.

Table 1 Baseline demographic and clinical characteristics, and potential risk factors for recurrence of included patients

Total number, *n*	706
Male gender, *n* (%)	186 (26.3)
Mean age, years ($\pm$ SD)	40.0 (16.3)
Principal sites of thrombosis, *n* (%)	Superior sagittal sinus 267 (37.8) Left lateral sinus 281 (39.8) Right lateral sinus 225 (31.9)
Concomitant intracranial hemorrhage, *n* (%)	197 (27.9)
Risk factors at first CVT, *n* (%)	Infections 59 (8.3) Trauma 18 (2.5) OC or HRT 278 (39.4) Pregnancy/puerperium 55 (7.8) Cancer or MPD 52 (7.4) Thrombophilic abnormalities (one at least) 290 (41.1) Severe thrombophilic abnormalities 83 (11.7) Unprovoked 312 (44.2)
Personal history of VTE, *n* (%)	54 (7.6)
Family history of VTE, *n* (%)	109 (15.4)
Acute antithrombotic therapy, *n* (%)	LMWH 443 (62.7) UFH 155 (21.9) Thrombolysis 11 (1.5) None 97 (13.7)
Post acute antithrombotic therapy, *n* (%)	Oral anticoagulants 590 (83.6) LMWH 37 (5.2) Acetyl salicylic acid 14 (2.0) None 62 (6.9)

CVT, cerebral vein thrombosis; HRT, hormone replacement therapy; LMWH, low-molecular-weight heparin; MPD, myeloproliferative disease; OC, oral contraceptives; UFH, unfractionated heparin; VTE, venous thromboembolic events.

Seventy-five patients (10.6%) were diagnosed with recurrent, non-fatal VTE. Clinical characteristics of patients with VTE recurrence are listed in Table 2. Recurrent events included recurrent CVT in 31 patients (4.4%) and VTE in other sites in the remaining 46 patients (6.5%). Two patients had a VTE and a concomitant recurrence of CVT. VTE in other sites occurred in the lower limbs in 30 patients, in the pulmonary arteries in six patients and in the lower limbs and pulmonary arteries at the same time in seven patients. Finally, three patients had a splanchnic vein thrombosis and 1 had a thrombosis of the upper limbs. Recurrence-free survival using the Kaplan–Meier method is represented in Fig. 1. The overall incidence of recurrent VTE was 23.6 per 1000 patient-years (95% CI 17.8–28.7). Most events occurred after anticoagulation discontinuation for an incidence of recurrence in this group of 35.1 events/1000 patient-years (95% CI, 27.7, 44.4). The recurrence rate was similar in patients with unprovoked CVT and in patients with CVT secondary to a known risk factors (22.8 events/1000 patient-years, 95% CI 15.9, 32.6 vs. 27.0 events/1000 patient-years, 95% CI 20.4, 36.0).

Table 2 Characteristics of patients with VTE recurrence

Total VTE recurrence, *n*	75
Mean Age, year (± SD)	36.9 (13.8)
Male gender, *n* (%)	22 (29.3)
CVT recurrence, *n* (%)	31 (4.4)
VTE (splanchnic thrombosis, deep venous thrombosis, pulmonary embolism) recurrence, *n* (%)	46 (6.5)
Principal sites of thrombosis, *n* (%)*	Superior sagittal sinus 40 (53.3) Left lateral sinus 29 (38.7) Right lateral sinus 26 (34.7)
Concomitant intracranial haemorrhage, *n* (%)	19 (25.3)
Risk factors at first CVT, *n* (%)	Infections 4 (5.3) Trauma 7 (9.3) OC or HRT 26 (34.7) Pregnancy/puerperium 8 (10.7) Cancer or MPD 8 (10.7) Thrombophilic abnormalities (one at least) 35 (46.7) Severe thrombophilic abnormalities (14.7) Idiopathic 30 (37.3)
Personal history of VTE, *n* (%)	14 (18.7)
Family history of VTE, *n* (%)	14 (18.7)

Two patients had both the recurrences. CVT, cerebral vein thrombosis; HRT, hormone replacement therapy; LMWH, low-molecular-weight heparin; MPD, myeloproliferative disease; OC, oral contraceptives; UFH, unfractionated heparin; VTE, venous thromboembolic events. *More than one site was involved in some patients.

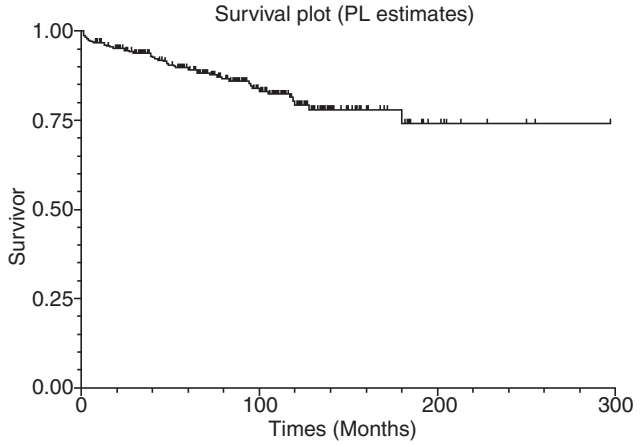

Fig. 1. Recurrence-free survival using the Kaplan–Meier method.

Cox proportional hazards models were fitted to identify covariates associated with time to VTE in patients with CVT. In the univariate model, a personal history of VTE (HR 2.73, 95% CI 1.53–4.89; $P < 0.001$), recent head trauma (HR 4.20, 95%CI 1.93–9.15; $P < 0.001$) and cancer (HR 2.57, 95% CI 0.91, 3.95; $P < 0.012$) were associated with recurrent VTE. Thrombophilia and severe thrombophilia were not associated with an increased risk of VTE recurrence. As a result of the controversial role of hyperhomocysteinaemia, we repeated the analysis excluding this thrombophilic abnormality; however, the results did not change (data not shown). Indefinite OAT was not associated with improved event free survival (Table 3). When all potential risk variables were included in a multivariate model, only a personal history of VTE remained significantly associated with recurrent CVT or VTE in other sites (HR 2.70; 95% CI 1.25–5.83; $P < 0.011$).

Table 3 Association of baseline characteristics and potential risk factor for recurrent VTE at univariate analysis

	HR	95% CI	*P*
Age at diagnosis	1.00	0.98–1.01	0.578
Gender	1.37	0.83–2.25	0.221
Personal history of VTE	2.73	1.53–4.89	0.001
Family history of VTE	1.14	0.63–2.00	0.669
Unprovoked presentation	1.02	0.61–1.69	0.926
Thrombophilic abnormalities	1.11	0.71–1.75	0.648
Severe thrombophilic abnormalities	1.16	0.61–2.20	0.654
OC/HRT	0.72	0.45–1.14	0.161
Cancer	2.57	0.91–3.95	0.012
Recent neurosurgery	1.71	0.24–12.4	0.594
Recent head trauma	4.20	1.93–9.15	< 0.001
Local or systemic infection	0.67	0.21–1.60	0.436
Myeloproliferative disease	2.03	0.28–14.60	0.483
Pregnancy/puerperium	1.05	0.48–2.28	0.911
Long-term anticoagulant therapy	1.13	0.65–1.95	0.664

HR, hazard ratio; CI, confidence interval.

Discussion

To our knowledge, this is the largest multicenter cohort study with an adequately long follow-up to evaluate the clinical history of patients with a first episode of CVT.

The principal finding of this study is in the estimate of anticipated rates of recurrent venous thromboembolic events, either CVT or VTE in other sites. During more than 3000 patient-years of follow-up, there were 31 episodes of CVT recurrence and 46 episodes of VTE in other sites, with an overall rate of 23.6 per 1000 patient-years and this rate was similar in patients with unprovoked CVT and in patients with CVT secondary to known risk factors. When recurrences were assessed only after OAT was stopped, the incidence rate was only slightly higher (35.1 events/1000 patient-years). These results provide a robust confirmation of previous observations [6,8]. In the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), the investigators observed 14 recurrent CVT events (2.2%) and 19 lower limb deep vein thrombosis or pulmonary embolism (3.0%) over a median follow-up period of 16 months [6]. More recently, Martinelli *et al.* [8] found an event rate of 2.03 per 100 patient-years in a population of 145 patients with a first episode of CVT. Although only a minority of patients were treated life long, substantially low rates of recurrent events were observed in this study. After multivariate analysis, a previous VTE, but not the duration of OAT, was associated with the risk of recurrence suggesting that long-term OAT may be not necessary in most CVT patients. Furthermore, in this study the presence of thrombophilia did not appear to be associated with an increased risk of VTE recurrence. This may be as a result of

a marginal effect of thrombophilic abnormalities on the risk of VTE recurrence, although other potential confounding factors, such as a different duration of anticoagulation in patients with specific thrombophilic abnormalities, could not be excluded. Thus, the role of thrombophila in CVT patients remains to be established. Many recurrent VTE occurred in women in which the first CVT occurred during pregnancy or puerperium or was secondary to OC or HRT use. However, neither female gender nor pregnancy/puerperium or the use of OC/HRT appeared to be an independent risk of VTE recurrence. Two previous studies have evaluated potential risk factors for recurrence in CVT patients [8,14]. In the study by Gosk-Bierska *et al*. [14], no variable was significantly associated with recurrent venous thrombosis in these patients, whereas in the study conducted by Martinelli *et al*. [8], risk factors for recurrent venous thrombosis were male gender and, for recurrence of VTE in other sites only, severe thrombophilia. These differences across studies may be because of differences in patient selection and to the smaller sample of the previous studies. For example, in the single center study by Martinelli *et al*. [8], all patients were referred for thrombophilia work-up and for counseling on the secondary prevention of VTE. In our study, participating centers had more heterogeneous roles in the management of CVT patients. Furthermore, taken together, the two studies by Gosk-Bierska and Martinelli enrolled a total of approximately 300 patients and may be underpowered to detect potential risk factors for recurrence.

This study also confirmed that most patients with CVT have a more benign prognosis than previously suspected: only 2.8% of patients had died at the end of the follow-up period and most surviving patients recovered completely or had only mild functional or cognitive deficit. This may be as a consequence of several factors. First, more sensitive diagnostic techniques have undoubtedly led to the detection of smaller thrombi, which probably have better prognosis. Second, older series included a higher proportion of patients with infection-associated CVT; these events are now less and less common as a result of the widespread use of antibiotics. Third, the widespread use of anticoagulant drugs for the acute and the long-term treatment of CVT has certainly contributed to improve the natural history of this disease. During follow-up, most patients had died as a result of underlying conditions such as cancer.

Although a formal comparison was not possible, CVT patients appear to have a lower risk of VTE recurrence in comparison to patients with DVT or PE [15]. This low risk may explain why many established risk factors for VTE recurrence in patients with a DVT or PE are not significant in CVT patients. Furthermore, these patients seem to have a more benign prognosis compared with patients with usual site thrombosis [15]. Differences in the baseline characteristics and in the concomitant diseases among these two populations may explain these results.

The present study has some limitations. First, the design of the study is retrospective. However, to overcome at least some of the limitations that are intrinsic to retrospective studies, we only involved centers where patients are regularly monitored and followed up, and to avoid misleading results we paid meticulous attention in the ascertainment of the reported outcome events and only patients with adequate quality of data or with available sources of documentation to complete missing information were considered eligible for inclusion. Second, a referral bias could not be excluded as we mainly enrolled patients who were started on OAT. Thus, the results of this study on the long-term outcome of the disease may not completely apply to the whole population of patients with CVT, as patients who died during the acute phase of the disease and patients who were deemed ineligible for long-term secondary prevention with anticoagulant drugs may be insufficiently represented. However, based on the results of previous studies [6,7] these patients should represent a small minority of CVT patients. Third, screening for thrombophilia was not systematically performed in all the patients. Thus, although the risk of recurrence in patients with mild thrombophilia did not appear to be increased, the results of this study on the role of thrombophilia should be interpreted with caution. Fourth, we have no reliable data on the recanalization rate in the whole group of CVT patients. Thus, we could not comment on its potential influence on the risk of VTE recurrence. Last and more important, a minority of patients with massive hemorrhages or other severe presentations may not have been included in this study as these patients may not be referred to the Thrombosis Units or Anticoagulation or Neurological Clinics. Thus, our population may have a slightly better prognosis compared with the general population of patients with CVT.

On the other hand, study strengths include the long duration of follow-up, both during anticoagulant treatment and after anticoagulant treatment withdrawal, and the large sample size of this cohort of patients, who had CVT diagnosed with objective methods and who were followed up homogeneously in a high number of centers.

In conclusion, the long-term risk of CVT recurrence and of VTE in other sites appears to be low in patients with a first episode of CVT, regardless of the duration of treatment. This risk appeared to be increased only in patients with previous VTE. The long-term prognosis of CVT in terms of mortality and residual disability is favorable in patients who survive the acute phase of disease.

Addendum

F. Dentali designed the study, collected, analyzed, performed statistical analysis and interpreted the data and drafted the paper; W. Ageno and D. Poli designed the study, collected analyzed and interpreted the data, drafted and reviewed the paper; U. Scoditti, M.N.D. di Minno, V.D. Stefano, S. Siragusa, M. Kostal, G. Palareti, M.T. Sartori, E. Grandone, M.C. Vedovati collected the data and reviewed the paper.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Appendix

Complete list of other authors and participating centers:

Anna Falanga, Teresa Lerede (Bergamo); Marina Bianchi (Como); Sophie Testa (Cremona); Dan Witt, Katie McCool (Denver, Colorado, USA); Eugenio Bucherini (Faenza); Elisa Grifoni (Firenze); Daniela Coalizzo (Foggia); Raffaella Benedetti (La Spezia); Marco Marietta (Modena); Maria Sessa, Clara Guaschino (Milano); Giovanni di Minno, Antonella Tufano (Napoli); Sofia Barbar (Padova); Alessandra Malato (Palermo); Mario Pini, Paola Castellini (Parma); Stefano Barco, Marisa Barone (Pavia); Maurizio Paciaroni, Andrea Alberti, Giancarlo Agnelli (Perugia); Matteo Giorgi Pierfranceschi (Piacenza); Petr Dulicek (Prague, Czech Republic); Mauro Silingardi, Landini Federica, Angelo Ghirarduzzi (Reggio Emilia); Eros Tiraferri (Rimini); Vincenzo di Lazzaro, Elena Rossi, Angela Ciminello (Roma); Samantha Pasca, Giovanni Barillari (Udine); Emanuele Rezoagli, Matteo Galli, Alessandro Squizzato (Varese); Alberto Tosetto (Vicenza)

All these authors collected and assembled the data, drafted the article, critically revised the article for important intellectual content and gave final approval of the article.

Table A1: Number of patients tested and results for each thrombophilic abnormality.

Thrombophilic abnormality	Tested, *N* (%)	Positive, *N* (%)
Total (one at least) (%)	627 (88.8)	290 (46.3)
Factor V Leiden, *n* (%)	560 (79.3)	51 (9.1)
G20210A prothrombin mutation	551 (78.0)	105 (19.1)
Protein C deficiency	552 (78.2)	18 (3.3)
Protein S deficiency	550 (77.8)	18 (3.3)
Antithrombin deficiency	564 (79.9)	11 (2.0)
Lupus anticoagulant	554 (78.5)	28 (5.1)
Anticardiolipin antibodies	556 (78.8)	18 (3.3)
Hyperhomocysteinemia	546 (77.3)	69 (12.6)
JAK2 V617F mutation	131 (25.9)	17 (13.0)

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