High Prevalence of *F2* 20210G > A in Splanchnic Vein Thrombosis and Cerebral Venous Sinus Thrombosis: A Retrospective Cohort Study of Patients with Thrombosis in Atypical Sites

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Abstract

Introduction Atypical sites for thrombosis include deep vein thrombosis (DVT) of the upper extremity (UE-DVT), splanchnic vein thrombosis (SVT), and cerebral venous sinus thrombosis (CVST). In addition to specific pathogenic factors, their underlying mechanisms share similarities with typical venous thromboembolism (VTE), namely, DVT of the lower extremity and/or pulmonary embolism, but are less understood.

Methods Records of unselected patients with a history of typical VTE ($n = 2{,}011$), UE-DVT ($n = 117$), SVT ($n = 83$), and CVST ($n = 82$), who were referred to the Institute in Bonn for ambulatory thrombophilia testing, were retrospectively analyzed. Acquired and hereditary thrombosis risk factors were comparatively assessed.

Results UE-DVT was characterized by a high rate (50.4%) of site-specific acquired risk factors. Compared with typical VTE, SVT was more frequently associated with systemic inflammation, infection, or malignancy (2.2 vs. 12.0%, $p = 3{\cdot}10^{-8}$) and the *JAK2* V617F mutation was present in 16.9%. In CVST compared with typical VTE, demographics and higher rates of oral contraception (43.2 vs. 57.6%, $p = 0.011$) and pregnancy (4.2 vs. 10.9%, $p = 0.012$) suggest a significant hormonal influence on etiology. While the prevalence of inhibitor deficiencies and factor V Leiden mutation did not differ between cohorts, the prevalence of *F2* 20210G > A was higher in SVT (15.7%, $p = 0.003$) and CVST (15.9%, $p = 0.003$) than in typical VTE (7.0%).

Conclusion The cohorts with thrombosis in atypical sites showed distinctive patterns of acquired risk factors. Further studies are warranted to provide additional mechanistic insight into the role of hormonal influence in CVST and the contribution of *F2* 20210G > A to the development of SVT and CVST.

Keywords

- cerebral venous sinus thrombosis
- splanchnic vein thrombosis
- thrombophilia
- upper extremity deep vein thrombosis
- venous thromboembolism

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received
April 9, 2024
accepted after revision
May 14, 2024

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Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/a-2329-1798.
ISSN 0720-9355.

Introduction

Thromboembolic conditions are the leading cause of mortality worldwide, with venous thromboembolism (VTE) being the second-most common after ischemic heart disease.[1] VTE includes deep vein thrombosis (DVT), pulmonary embolism (PE), and the combination thereof. Considering only lower-extremity DVT, the most common site for VTE, the estimated annual incidence rates of VTE range from 104 to 183 per 100,000 person-years in people of European ancestry.[2] The incidence of DVT of the upper extremity (UE-DVT) is considerably lower, as only 4 to 14% of all cases of DVT are estimated to be localized at this site.[3,4] Other atypical sites of venous thrombosis include the splanchnic veins and the cerebral venous sinuses.[5,6] For portal vein thrombosis, the most common manifestation of splanchnic vein thrombosis (SVT), incidence rates of approximately 2 to 4 per 100,000 person-years have been reported, whereas the annual incidence of Budd–Chiari syndrome, the least common manifestation, has been estimated to be 1 to 2 per million.[7–9] Cerebral venous sinus thrombosis (CVST) has an estimated annual incidence of 3 to 4 per million.[6]

The pathomechanism of VTE is multifactorial and includes acquired risk factors like surgery, pregnancy, or malignant disease, as well as hereditary risk factors such as deficiencies of coagulation inhibitors, the factor V Leiden (FVL) mutation, or the prothrombin (*F2*) gene 20210G > A mutation.[10] There are additional, specific risk factors that come into play in the development of thromboses in atypical sites, for example, venous catheters causing UE-DVT,[11] SVT in the setting of myeloproliferative neoplasms,[12] and CVST associated with mastoiditis or sinus infection.[13] While the role of various acquired and hereditary risk factors in the pathogenesis of typical VTE is well established, comparative studies covering several atypical sites of venous thrombosis simultaneously are scarce.[14–16]

The objective of this study was to characterize and compare the risk profiles of thrombosis at atypical sites. Therefore, we assessed the rates of acquired and hereditary risk factors (both specific and nonspecific to the site of VTE) in patients with a history of UE-DVT, SVT, or CVST as compared to a reference cohort of patients with VTE with typical localization.

Methods

This retrospective, observational cohort study was conducted at the University Hospital Bonn. The study included data from patients who visited the thrombophilia clinic of our institution between January 2008 and December 2019. Ethics approval was sanctioned by the Institutional Review Board and Ethics Committee of the Medical Faculty of the University of Bonn, and the study was conducted in accordance with the declaration of Helsinki. Study participants gave their written informed consent.

Identification and Inclusion of Patients

A total of 4,578 patients were identified as first-time referrals for thrombophilia screening within the aforementioned period. After the exclusion of 1,832 patients without a history of thrombosis who mostly underwent thrombophilia screening due to a family history of thrombosis or thrombophilia, or due to pregnancy complications, the remaining 2,746 cases were further analyzed. Results of thrombophilia testing were retrieved from the database of our laboratory information system. Demographical and clinical data were extracted from the medical records. Inclusion criteria were a history of VTE, SVT, or CVST confirmed by suitable imaging diagnostics. VTE included DVT of the lower extremity (excluding isolated inferior vena cava thrombosis), UE-DVT (including thrombosis of the brachial, axillary, subclavian, internal jugular, radial, and ulnar veins), and isolated PE. SVT included thrombosis of the splenic, mesenteric, and portal veins, as well as Budd–Chiari syndrome. CVST included thrombosis of the cerebral veins and dural sinuses. Nineteen patients aged <18 years at the time of referral were excluded, in addition to 434 patients with thrombosis types other than those defined above as the sole manifestations of thrombosis, including myocardial infarction, ischemic stroke, other arterial thrombosis, retinal thrombosis, and superficial vein thrombosis. The final study population included 2,293 patients who were subdivided into four cohorts: (1) patients with typical VTE, that is, lower extremity DVT, PE, or the combination thereof ($n = 2{,}011$); (2) patients with UE-DVT ($n = 117$); (3) patients with SVT ($n = 83$); and (4) patients with CVST ($n = 82$). A diagram of patient inclusion is shown in ►Fig. 1.

Thrombophilia Screening

Thrombophilia screening always included genetic testing for the FVL and *F2* 20210G > A mutations using in-house methods described previously,[17,18] as well as measurement of plasma levels of antithrombin (AT), protein C (PC), and protein S (PS) using commercially available assays. If the results of the latter were suspicious for hereditary inhibitor deficiency, the diagnosis was confirmed via genetic testing. Antiphospholipid antibody testing was also performed; however, the results were not included in the analysis because the results of confirmatory testing at least 12 weeks apart were not available in all cases, and moreover, we did not want to limit the study to patients with thrombotic events that occurred within 5 years prior to the first visit.[19]

Clinical Parameters

In addition to the history of thrombosis, clinical parameters collected for analysis included sex (male or female), body mass index (BMI) at the time of the visit, age, and acquired risk factors present at the time of the first event that defined allocation to one of the four study cohorts. For example, if a patient suffered from lower extremity DVT during pregnancy and some years later from spontaneous CVST, she was allocated to the CVST cohort, and no acquired risk factor was documented. Acquired thrombosis risk factors were grouped into site-specific and non–site-specific risk factors, the latter including oral contraception, pregnancy, immobilization, surgery, as well as systemic inflammation, infection, and malignancy. Site-specific acquired risk factors included site-specific surgery or

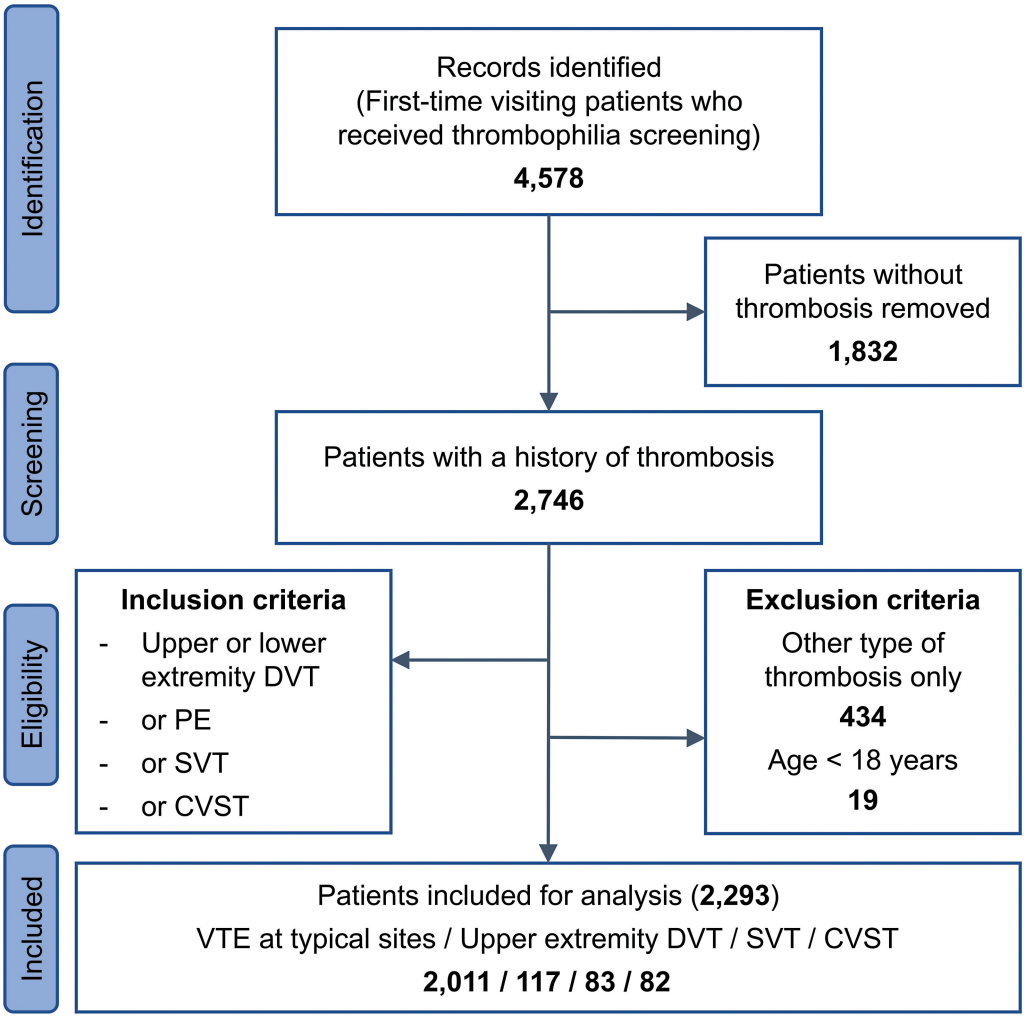

Fig. 1 Study flow chart. Thrombophilia screening included testing for deficiencies of antithrombin, protein C, protein S, factor V Leiden, and *F2* 20210G > A mutation. Other types of thrombosis included arterial thrombosis, retinal thrombosis, and superficial vein thrombosis, and patients were excluded if they did not have upper or lower extremity deep vein thrombosis (DVT), pulmonary embolism (PE), splanchnic vein thrombosis (SVT), or cerebral venous sinus thrombosis (CVST) as sole or additional thrombotic events.

injury, vascular malformation, local inflammation, infection, or malignancy, as well as the Janus kinase 2 (*JAK2*) V617F mutation, which was assessed in all patients in the SVT cohort and in selected patients in the CVST cohort ($n = 4$). It was further noted whether an UE-DVT was effort related, catheter related, or associated with thoracic-inlet syndrome.

Statistical Analysis

Continuous data are presented as the median and interquartile range (IQR) after testing for normality using the Shapiro–Wilk test. To compare continuous data between the cohorts of patients with thrombosis in atypical sites and the cohort of patients with VTE in typical sites, the Mann–Whitney test was used. Frequency data were compared using the chi-square test. The Yates correction was performed in case of cell frequencies below 5. p-values ≤ 0.05 were considered statistically significant. We did not correct for multiple comparisons due to the hypothesis-generating character of our study. All calculations were performed using the XLSTAT statistical and data analysis solution software (Addinsoft, Boston, Massachusetts, United States).

Results

►Table 1 shows the distribution of thrombotic events in typical and atypical sites in the study population. Thirty (25.6%) patients with UE-DVT, 23 (27.7%) patients with SVT, and 13 (15.9%) patients with CVST also had a history of VTE in typical sites. The recurrence rate was 27.8% in patients with typical VTE, 8.5% in patients with UE-DVT, 13.3% in patients with SVT, and 2.4% in patients with CVST.

Comparison of Acquired Risk Factors

►Table 2 shows the comparison of demographic data and rates of non–site-specific acquired thrombosis risk factors in the study population. The proportion of female patients was higher in the cohorts with UE-DVT (67.5%, $p = 0.002$) and CVST (78.0%, $p = 9{\cdot}10^{-6}$) as compared to the cohort with typical VTE localization (53.2%). Patients in both former cohorts were also younger at the time of the first event (median age of 44 years, $p = 0.049$ and 31 years, $p = 10^{-4}$, respectively) and had a lower BMI (25.9 kg/m^2, $p = 7{\cdot}10^{-4}$ and 25.2 kg/m^2, $p = 10^{-4}$, respectively) than in the latter (47

Table 1 Thrombotic events

	Typical VTE[a]	DVT of the upper extremity	SVT[b]	CVST
Patients	2,011	117	83	82
Patients with typical VTE[b]	2,011 (100%)	30 (25.6%)	23 (27.7%)	13 (15.9%)
Patients with recurrent VTE	559 (27.8%)	12 (10.3%)	8 (9.6%)	–
Patients with arterial events[c]	104 (5.2%)	8 (6.8%)	5 (6.0%)	1 (1.2%)
Recurrent atypical thrombosis	–	10 (8.5%)	11 (13.3%)	2 (2.4%)
Typical VTE events[b]	2,702	55	39	13
Events of isolated DVT	1,617 (59.8%)	38 (59.1%)	26 (66.7%)	10 (76.9%)
Events of isolated PE	496 (18.4%)	8 (14.5%)	5 (12.8%)	–
Events of DVT with PE	589 (21.8%)	9 (16.4%)	8 (20.5%)	3 (23.1%)

Abbreviations: CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; PE, pulmonary embolism; SVT, splanchnic vein thrombosis; VTE, venous thromboembolism.
[a]DVT of the lower extremity and/or pulmonary embolism.
[b]Thereof 26 with portal vein thrombosis, 15 with mesenterial vein thrombosis, 3 with splenic vein thrombosis, 38 with a combination thereof, and 1 with Budd–Chiari syndrome (PE).
[c]Ischemic stroke, myocardial infarction, peripheral arterial thrombosis.

Table 2 Demographics and non–site-specific acquired thrombosis risk factors

	Typical VTE ($n = 2,011$)	Upper extremity DVT ($n = 117$)	SVT ($n = 83$)	CVST ($n = 82$)
Male/Female	942/1,069	38/79	47/36	18/64
p	–	0.002	0.080	$9{\cdot}10^{-6}$
Age at first event, years, median (IQR)	47 (33–59)	44 (32–52)	48 (39–58)	31 (23–43)
p	–	0.049	0.374	10^{-4}
BMI, kg/m^2, median (IQR)	27.6 (24.5-31.1)	25.9 (23.1-28.8)	25.9 (24.0-30.1)	25.2 (21.7-29.0)
p	–	$7{\cdot}10^{-4}$	0.054	10^{-4}
Non–site-specific acquired risk factors, total	737 (36.6%)	56 (47.9%)	34 (41.0%)	56 (68.3%)
p	–	0.015	0.424	$7{\cdot}10^{-9}$
Oral contraception (percentage in females)	462 (43.2%)	30 (38.0%)	15 (44.1%)	38 (57.6%)
p	–	0.363	0.853	0.011)
Pregnancy (percentage in females)	45 (4.2%)	4 (5.1%)	–	7 (10.9%)
p	–	0.941	0.408	0.012
Immobilization	68 (3.4%)	2 (1.7%)	1 (1.2%)	1 (1.2%)
p	–	0.472	0.438	0.448)
Surgery	118 (5.9%)	14 (12.0%)	8 (9.6%)	4 (4.9%)
p	–	0.008	0.157	0.893
Systemic inflammation, infection, malignancy[a]	44 (2.2%)	6 (5.1%)	10 (12.0%)	6 (7.3%)
p	–	0.041	$3{\cdot}10^{-8}$	0.003

Abbreviations: BMI, body mass index; CI, confidence interval; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; SVT, splanchnic vein thrombosis; VTE, venous thromboembolism.
Notes: *p*-values describe differences between patients with VTE in typical and atypical sites and were calculated using the chi-square test for dichotomous variables, and the Mann–Whitney test for age and BMI.
[a]Malignancy other than myeloproliferative neoplasms.

years, 27.6 kg/m^2). The overall percentage of patients with non–site-specific acquired risk factors at the time of the thrombosis was also higher in the cohort with UE-DVT (47.9%, $p = 0.015$) and in the CVST cohort (68.3%, $p = 7{\cdot}10^{-9}$) than in the cohort with typical VTE (36.6%). The rates of oral contraceptive use and pregnancy were higher in the CVST group than in patients with typical VTE, with 57.6 versus 43.2% ($p = 0.011$) and 10.9 versus 4.2% ($p = 0.012$), respectively. UE-DVT was more frequently associated with surgery than VTE in typical sites (12.0 vs. 5.9%, $p = 0.008$). The rate of systemic inflammation, infection, or malignant disease was significantly higher in all three cohorts with thrombosis in

Table 3 Site-specific acquired thrombosis risk factors

	Upper extremity DVT ($n = 117$)	SVT ($n = 83$)	CVST ($n = 82$)
Site-specific surgery or injury	4 (3.4%)	2 (2.4%)	–
Vascular malformation	2 (1.7%)	1 (1.2%)	–
Local inflammation, infection, malignancy	6 (5.1%)	6 (7.2%)	3 (3.7%)
JAK2 V617F mutation	–	14 (16.9%)	1 (1.2%)
Effort	4 (3.4%)	–	–
Catheter	35 (29.9%)	–	–
Thoracic-inlet syndrome	8 (6.8%)	–	–
Total	59 (50.4%)	23 (27.7%)	4 (4.9%)

Abbreviations: CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; *JAK2*, Janus kinase 2; SVT, splanchnic vein thrombosis.

atypical sites than in the group with typical VTE localization (2.2%), with 5.1% ($p = 0.041$) in the cohort with UE-DVT, 12.0% ($p = 3{\cdot}10^{-8}$) in the SVT cohort, and 7.3% ($p = 0.003$) in the cohort with CVST. Aside from this, the SVT cohort and the cohort with typical VTE did not differ from one another with regard to demographic factors and the rates of non–site-specific acquired risk factors for thrombosis.

The percentage of patients with site-specific acquired risk factors was 50.4% in the UE-DVT cohort, 27.7% in the SVT cohort, and 4.9% in the CVST cohort (►**Table 3**). The most frequent site-specific risk factors in these respective groups were indwelling catheters (29.9%), the *JAK2* V617F mutation (16.9%), and local inflammation or infection (two cases of maxillary sinusitis and one case of mastoiditis, 3.7%; ►**Table 3**).

Comparison of Hereditary Risk Factors

►**Table 4** shows the prevalence of classic hereditary thrombophilia in the study population. The rates of hereditary deficiencies of AT, PC, and PS, as well as FVL did not differ significantly between cohorts. However, the rates of *F2* 20210G > A mutation were higher in the cohorts of patients with SVT (15.7%, $p = 0.003$) and CVST (15.9%, $p = 0.003$) than in patients with typical VTE (7.0%). In the SVT cohort, this difference was driven by a higher rate of heterozygous *F2*

Table 4 Hereditary thrombophilia

	Typical VTE ($n = 2{,}011$)	Upper extremity DVT ($n = 117$)	SVT ($n = 83$)	CVST ($n = 82$)
Deficiency of antithrombin, protein C, protein S	61[a] (3.0%)	4[b] (3.4%)	1[c] (1.2%)	3[d] (3.7%)
p	–	0.967	0.527	0.996
FV Leiden, total	447 (22.2%)	29 (24.8%)	17 (20.5%)	18 (22.0%)
p	–	0.519	0.707	0.953
FV Leiden, homozygous	31 (1.5%)	2 (1.7%)	1 (1.2%)	–
p	–	0.809	0.833	0.505
FV Leiden, heterozygous	389 (19.3%)	25 (21.4%)	13 (15.7%)	14 (17.1%)
p	–	0.591	0.404	0.609
F2 20210G > A, total	141 (7.0%)	9 (7.7%)	13 (15.7%)	13 (15.9%)
p	–	0.780	0.003	0.003
F2 20210G > A, homozygous	3 (0.1%)	–	1 (1.2%)	1 (1.2%)
p	–	0.396	0.381	0.376
F2 20210G > A, heterozygous	111 (5.5%)	7 (6.0%)	9 (10.8%)	8 (9.8%)
p	–	0.831	0.041	0.104
FV Leiden and *F2* 20210G > A, both heterozygous	27 (1.3%)	2 (1.7%)	3 (3.6%)	4 (4.9%)
p	–	0.938	0.217	0.033

Abbreviations: AT, antithrombin; CI, confidence interval; CVST, cerebral venous sinus thrombosis; DVT, deep vein thrombosis; PC, protein C; PS, protein S; SVT, splanchnic vein thrombosis; VTE, venous thromboembolism.
Notes: *p*-values describe differences between patients with VTE in typical and atypical sites and were calculated using the chi-square test.
[a]AT ($n = 11$), PC ($n = 32$), PS ($n = 18$).
[b]AT, PC ($n = 2$ each).
[c]PC.
[d]AT, PC, PS ($n = 1$ each).

20210G > A carriers as compared to the cohort with typical VTE localization (10.8 vs. 5.5%, $p = 0.041$), whereas in the CVST cohort there was a higher prevalence of combined heterozygous FVL and *F2* 20210G > A mutations (4.9 vs. 1.3%, $p = 0.033$) compared to the cohort with typical VTE.

Discussion

In this study, risk profiles of patients with thrombosis in typical sites and various atypical sites were compared, with all cohorts derived from the same population of referrals to our ambulatory thrombophilia clinic. We considered that this approach would have an advantage over studies in which only one type of atypical thrombosis was assessed against typical VTE because the use of the same reference cohort with typical VTE would make the risk profiles of different types of atypical thrombosis more distinguishable. Therefore, we also deliberately decided against a matched-pairs design.

In the three cohorts with thrombosis localized in atypical sites, distinctive patterns of acquired risk factors were observed. In the case of UE-DVT, site-specific acquired risk factors were most common. Associations of indwelling venous catheters (observed in 29.9% of our patients) and inflammation, infection, or malignancy (10.2% when combining non–site-specific and local manifestations) with UE-DVT have been previously described.[4,15,20–23] The observed higher rate of patients with surgery-related thrombotic events or systemic inflammation, infection, or malignancy who developed atypically localized thrombosis in comparison to the cohort with typical VTE in our study could also possibly be explained by venous catheters or venous punctures being common in these patient groups. Strenuous effort and thoracic inlet syndrome are other well-established specific risk factors for UE-DVT,[20,21,24] which our study findings support. Furthermore, this cohort was slightly younger, more female, and consequently showed a lower BMI than the cohort with typical VTE. Higher rates of women with UE-DVT have been observed previously,[15,21] while others have reported a higher incidence in men.[22] In agreement with previous studies, the rates of the well-established thrombotic risk factors of oral contraceptive use, pregnancy, and immobilization were not increased in our patients with UE-DVT as compared to the cohort with typical VTE.[15,21]

The most common acquired conditions in our SVT cohort were the *JAK2* mutation along with systematic and local inflammation, infection, or malignancy, which are established risk factors for SVT.[5,25] Demographic features and rates of non–site-specific acquired risk factors did not differ between the SVT cohort and the reference cohort with typical VTE. This is largely in agreement with a previous study in a larger population which compared patients with SVT ($n = 341$) and lower extremity DVT ($n = 3,621$), in which there were no observed differences regarding sex, pregnancy, and recent surgery.[26] Of note, in this previous study, the patients with SVT were slightly younger than those in the DVT cohort.

In patients with CVST, the rate of site-specific thrombosis risk factors was the lowest among the three cohorts with atypical thrombosis (4.9%, three of four cases with local infections). However, we observed a pattern of acquired risk factors that included a younger age, a higher proportion of women, and consecutively a lower BMI, as well as higher rates of oral contraceptive use and pregnancy. A similar risk profile in patients with CVST has been reported in previous studies.[27–29] In addition, our findings of an increased rate of inflammation, infection, and malignancy in the CSVT cohort in comparison to patients with typical VTE are also in agreement with a larger, previous study.[28] Although pregnancy and the use of hormonal contraceptives are established risk factors for thrombosis, an especially high risk for CVST could not be explained by our current understanding of the changes in hemostasis during pregnancy or oral contraceptive use.[30,31]

Among the hereditary thrombophilias that were assessed, significant differences between the cohorts with thrombosis in atypical sites and patients with typical VTE were observed only for the prevalence of *F2* 20210G > A, which was higher in the SVT and CVST cohorts but not in the cohort with UE-DVT. For patients with CVST and UE-DVT, this observation is in agreement with previous studies; a large meta-analysis has shown that *F2* 20210G > A is a risk factor for CVST,[27] and a higher rate of *F2* 20210G > A but not FVL in CVST compared to lower extremity DVT has been reported previously.[28] By contrast, a higher rate of *F2* 20210G > A in UE-DVT than lower extremity DVT has not been reported.[15,21] The evidence regarding increased prevalence of *F2* 20210G > A in SVT is conflicting. While some studies, including ours, have observed a higher rate of *F2* 20210G > A in SVT than in DVT,[25,32,33] this was not reported by others.[25,26]

Although our observational study does not provide mechanistic insight, it is tempting to speculate about explanations for a possibly increased thrombogenicity of *F2* 20210G > A in the splanchnic and cerebral vein systems. The prothrombotic effect of the *F2* 20210G > A mutation lies in the increased prothrombin levels in the circulation.[34] It is conceivable that increased prothrombin synthesis could make its main synthesis site in the liver a predilection site for thrombosis. Our current understanding of coagulation in liver disease is a rebalanced hemostasis, which is sensitive to prothrombotic or prohemorrhagic stimuli.[35,36] This would make patients with liver disease, in whom splanchnic vein thrombosis is common,[5] especially susceptible to thrombosis if they are *F2* 20210G > A carriers. Ample amounts of prothrombin are also present in neural tissue,[37,38] and might come into contact with circulating blood in situations associated with CVST, including dural arteriovenous fistulae, meningitis, neurosurgical procedures, or trauma.[28,39]

Limitations of our study include its single-center design, retrospective nature, and potential referral bias. In addition, some risk factors were not assessed in all patients, and not all established thrombophilic risk factors could be studied. Multicenter studies on thrombosis in atypical sites are rare and the majority of studies in the field are single-center studies that focus only on one type of atypical thrombosis. As our study

population consisted of patients who were preselected by their referring physicians, it may not be representative. This effect is somewhat mitigated because a potential referral bias should be similar in the patient groups with thrombosis in atypical sites and the reference cohort with typical VTE. One risk factor that was not assessed in every patient of the study population was the *JAK2* V617F mutation, which was studied in the SVT cohort and some patients in the CVST cohort, but not in patients with UE-DVT or typical VTE. Another risk factor that was assessed differently in patients with thrombosis in atypical sites and VTE in typical sites was site-specific surgery or trauma. In the cohort with typical VTE, we did not differentiate whether a surgical procedure was performed on the leg where the DVT was situated, or elsewhere. Furthermore, patients with isolated PE were categorized as having a VTE in a typical site—which is in line with the definition for isolated PE—although in some cases, the PE might have been caused by UE-DVT. Established thrombotic risk factors that we did not evaluate as part of the study analysis were the presence of antiphospholipid antibodies, smoking, long-distance travel, or the family history.

In conclusion, we observed distinctive patterns of acquired and hereditary risk factors in UE-DVT, SVT, and CVST. Overall, hereditary risk factors were not less common in patients with thrombosis in atypical sites than in those with VTE in typical sites, and the *F2* 20210G > A mutation was more prevalent in SVT and CVST than in the other two cohorts. These findings support the screening for hereditary thrombophilic risk factors in patients with thrombosis in the atypical sites covered by our study. Larger, multicentric studies are needed to better characterize the risk profiles in patients with atypical thrombosis. Also warranted are studies investigating the potential underlying mechanisms of a specific hormonal contribution to the pathogenesis of CVST, as well as the contribution of *F2* 20210G > A mutation to the development of SVT and CVST.

What Is Known About This Topic?

- Atypical site thromboses include upper extremity thrombosis, splanchnic vein thrombosis (SVT), and cerebral venous thrombosis (CVST).
- Their underlying risk factors are less understood than for thrombosis in typical sites.

What Does This Paper Add?

- Thromboses in atypical sites show distinct patterns of risk factors.
- Hormonal influence appears to play a major role in CVST.
- Prothrombin 20210G > A might be more prevalent in CVST and SVT than in thrombosis in typical sites.

Authors' Contributions

H.R. and S.R. are joint senior authors. H.R. and S.R. conceived and designed the study; D.K., H.L.M, N.S., and S.R. collected the data; D.K., H.R., and S.R. analyzed the data. D.K., H.R., and S.R. drafted and edited the manuscript. All authors revised the manuscript, agreed with its content, and approved of submission.

Declaration of Competing Interest

J.O. has received research funding from Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Swedish Orphan Biovitrum, and Takeda; consultancy, speakers bureau, honoraria, scientific advisory board, and travel expenses from Bayer, Biogen Idec, BioMarin, Biotest, Chugai Pharmaceutical Co., Ltd., CSL Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd., Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum, and Takeda. The other authors declare no competing financial interests.

Conflict of Interest

JO: Grants or contracts from any entity: Bayer, Biotest, CSL Behring, Octapharma, Pfizer, Swedish Orphan Biovitrum, and Takeda. Consulting fees: Bayer, Biogen Idec, BioMarin, Biotest, Chugai Pharmaceutical Co., Ltd., CSL Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd., Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum, and Takeda. Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Bayer, Biogen Idec, BioMarin, Biotest, Chugai Pharmaceutical Co., Ltd., CSL Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd., Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum, and Takeda. Support for attending meetings and/or travel: Bayer, Biogen Idec, BioMarin, Biotest, Chugai Pharmaceutical Co., Ltd., CSL Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd., Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum, and Takeda. Participation on a Data Safety Monitoring Board or Advisory Board: Bayer, Biogen Idec, BioMarin, Biotest, Chugai Pharmaceutical Co., Ltd., CSL Behring, Freeline, Grifols, LFB, Novo Nordisk, Octapharma, Pfizer, F. Hoffmann-La Roche Ltd., Sanofi, Spark Therapeutics, Swedish Orphan Biovitrum, and Takeda.
The other authors have no conflict of interest.

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