Received: 8 June 2022 | Accepted: 19 July 2022

DOI: 10.1111/jth.15834

RESEARCH LETTER

Site-specific venous thrombosis in essential thrombocythemia: Impact on subsequent vascular events and survival

To the editor,

Major venous thrombosis in essential thrombocythemia (ET), with an estimated incidence of 0.6 per 100 patient-years, accounts for one third of all thrombotic events.[1] In addition, the incidence of major hemorrhage is estimated at 0.79 per 100 patient-years.[2] A recent systematic review highlighted the variable risk of recurrent venous events in myeloproliferative neoplasms (MPN), which ranges from 0% to 33%.[3] Age > 60 years, thrombosis history, and *JAK2* mutation are established risk factors for venous thrombosis in ET.[4] Thrombosis and survival assessments by the International Prognostic Score for Essential Thrombocythemia (IPSET) consider thrombosis history without accounting for site, along with age > 60 years and *JAK2* mutation (revised IPSET-thrombosis) or leukocytosis $\geq 11 \times 10^9$/L (IPSET-survival).[4,5] Regardless of the association of splanchnic and cerebral venous thrombosis with recurrence, impact on overall survival is unknown.[6,7] The current study focuses on venous thrombosis in ET with the following objectives: (1) describe the site-specific prevalence, phenotypic, and genotypic correlations; (2) determine risks of recurrent venous thrombosis and major hemorrhage; and (3) evaluate the prognostic impact of venous thrombosis on overall survival, fibrotic and leukemic transformation, and arterial events.

The current retrospective series was conducted following institutional review board approval and included 737 adult patients with ET evaluated at the Mayo Clinic from 1967–2021 and confirmed to fulfill the 2016 World Health Organization (WHO) criteria.[8] Follow-up information including vascular events and disease progression was updated in May 2021. Patients with major venous thrombosis confirmed on imaging studies were stratified into three cohorts based on first event: cerebral venous thrombosis (CVT); splanchnic venous thrombosis (SVT) inclusive of hepatic, portal, splenic and mesenteric venous thrombosis; and other venous thrombosis (other VT), the latter included deep venous thrombosis, pulmonary embolism, and central retinal vein thrombosis. Comparison between categorical variables was performed by chi square test and continuous variables by Wilcoxon/Kruskal–Wallis tests. A Cox proportional hazards model was used to compute multivariable analyses. *p*-value ≤.05 was considered significant. JMP Pro 16.0.0 software package (SAS Institute) was utilized for all analyses.

Of 737 patients with ET (median age 58 years, range 18–90; 63% females), first major venous thrombosis was documented in 131 (18%; 2 per 100 patient-years) with 35 (27%), 48 (37%), and 48 (37%) events prior to, at, or after ET diagnosis, respectively, and were provoked in 42 (32%) cases in the context of surgery ($n = 24$), immobilization/trauma ($n = 5$), pregnancy ($n = 5$), solid tumor ($n = 4$), hospitalization ($n = 3$), or oral contraceptive use ($n = 1$). Site-specific frequencies were 2% ($n = 16$), 5% ($n = 38$), and 11% ($n = 77$) for CVT, SVT, and other VT, respectively. Table 1 outlines presenting clinical and laboratory features including phenotypic and genotypic comparison of ET patients with CVT, SVT, versus other VT. Patients with CVT in comparison to those with other VT were more likely to be younger (median age 39 vs. 67 years; $p = .02$), display lower platelet count (median 624 vs. 789×10^9/L; $p = .0003$), and less likely to have hypertension (6% vs. 58%, $p = .01$) or smoking history (0% vs. 30%; $p = .02$; Table 1). *JAK2*V617F mutational frequency, albeit higher with CVT and SVT, did not significantly differ from those with other VT (83% and 82% vs. 69%; $p = .6$ and $p = .1$, respectively). On the other hand, SVT patients compared to those with other VT, were more likely to be younger (median age; 40 vs. 67 years, $p = .0001$), present with major hemorrhage prior to/at the time of ET diagnosis (24% vs. 8%, $p = .03$) and less likely to be *CALR* mutated (7% vs. 23%, $p = .03$). In addition, the incidence of *CALR* mutation was lower in patients with VT versus those without VT (17% vs. 28%, $p = .05$). Next generation sequencing investigated the presence of high-risk molecular variants: *SRSF2*, *U2AF1*, *ASXL1*, *EZH2*, and *IDH2*. *SRSF2*, *ASXL1*, and *IDH2* mutations were present in one (3%), three (8%), and one (3%) patients, respectively.

Treatments for CVT, SVT, and other VT included systemic anticoagulation alone (0%/28%/33%), systemic anticoagulation plus cytoreductive therapy (50%/28%/31%), systemic anticoagulation plus aspirin (30%/6%/9%), systemic anticoagulation plus aspirin and cytoreductive therapy (10%/9%/17%), aspirin and/or cytoreductive therapy (10%/19%/5%). Warfarin was utilized in 49 (51%) of patients,

Manuscript handled by: Jeffrey Zwicker

Final decision: Jeffrey Zwicker, 19 July 2022

TABLE 1 Presenting clinical and laboratory characteristics of 737 patients with essential thrombocythemia (ET) stratified by first major venous thrombotic event

Variables	All patients *n* = 737	No venous thrombosis (VT) (anytime) *n* (%) 606 (82)	Venous thrombosis (VT) (anytime) *n* (%) 131 (18) At or prior to diagnosis, *n* = 83	Cerebral venous thrombosis (CVT) (anytime) *n* (%) 16 (2) At or prior to diagnosis, *n* = 15
Median age (range), years	58 (18–90)	58 (18–90)	56 (18–89)	39 (18–85)
Age > 60 years, *n* (%)	340 (46)	278 (46)	62 (47)	2 (13)
Female, *n* (%)	464 (63)	384 (63)	80 (61)	9 (56)
Hemoglobin, median (range), g/dl	13.8 (9–16.3)	13.9 (11–16.3)	13.6 (9–16.1)	13.5 (10.2–15.7)
Leukocytes, median (range), $\times 10^9$/L	9 (4–32)	9 (4–28)	9 (4–32)	6 (5–11)
Leukocytes ≥ 11×10^9/L, *n* (%)	157/724 (22)	130/599 (22)	27/125 (22)	0
Platelets, median (range), $\times 10^9$/L	800 (230–3460)	809 (434–3460)	730 (230–3330)	624 (427–1072)
Cardiovascular risk factors, *n* (%)	364/681 (53)	291/551 (53)	73/130 (56)	1/16 (6)
Diabetes mellitus	61/679 (9)	49/549 (9)	12/130 (9)	0
Hypertension	279/680 (41)	226/550 (41)	53/130 (41)	1/16) (6)
Smoking	160/676 (24)	124/546 (23)	36/130 (28)	0
Driver mutation status, *n* (%)	*n* = 733	*n* = 606	*n* = 127	*n* = 12
JAK2V617F	445 (61)	351 (58)	94 (74)	10 (83)
CALR	194 (26)	172 (28)	22 (17)	1 (8)
MPL	20 (3)	19 (3)	1 (1)	0
Triple negative (TN)	74 (10)	64 (11)	10 (8)	1 (8)
Next generation sequencing, *n* (%)	*n* = 245	*n* = 206	*n* = 39	*n* = 2
SF3B1	6	5	1	0
SRSF2	7	6	1	0
U2AF1	2	2	0	0
ASXL1	12	9	3	0
EZH2	3	3	0	0
IDH2	3	2	1	0
TP53	4	3	1	0
SH2B3	1	0	1	0
DNMT3A	16	14	2	0
TET2	21	14	7	0
CSF3R	2	2	0	0
RUNX1	2	2	0	0
Thrombophilia[c], *n* (%)			5/111 (5)	2/15 (14)
Antiphospholipid antibody			2/111 (2)	1/15 (7)
Prothrombin G20210A (HET)			1/111 (0.5)	1/15 (7)
Factor V Leiden (HET)			2/111 (2)	0
Revised IPSET-thrombosis[d], *n* (%)	*n* = 737	*n* = 606	*n* = 131	*n* = 16
Very low	167 (23)	155 (26)	12 (9)	0
Low	167 (23)	155 (26)	12 (9)	1 (6)
Intermediate	85 (11)	81 (13)	4 (3)	0
High	318 (43)	215 (35)	103 (79)	15 (94)
Major arterial thrombosis at or prior to ET diagnosis[b], *n* (%)	96 (13)	72 (12)	24 (18)	2 (13)
Major arterial thrombosis after ET diagnosis[b], *n* (%)	109 (15)	82 (13)	27 (21)	1 (6)
Major hemorrhage at or prior to ET diagnosis[e], *n* (%)	41/720 (6)	24/592 (4)	17/128 (13)	2/16 (13)
Major hemorrhage after ET diagnosis[e], *n* (%)	85/720 (12)	56/592 (9)	29/128 (23)	1/16 (6)

Note: *p* Values < .05 are significant and in bold.

[a]Other venous thrombosis includes deep venous thrombosis (*n* = 43), pulmonary embolism (*n* = 20), deep venous thrombosis and pulmonary embolism (*n* = 12), and retinal vein thrombosis (*n* = 2).

[b]Major arterial thrombosis includes myocardial infarction, angina, cerebrovascular accidents, transient ischemic attack, peripheral arterial thrombosis, aortic thrombosis, mesenteric artery thrombosis, central retinal thrombosis.

[c]Thrombophilia testing included Factor V Leiden, prothrombin gene mutation, Protein C, S, Antithrombin deficiency, anti-phospholipid antibody, paroxysmal nocturnal hemoglobinuria (PNH).

[d]International Prognostic Score for thrombosis in Essential Thrombocythemia (IPSET-thrombosis).

[e]Major hemorrhage includes bleeding events that require red cell transfusion support, resulted in ≥2 g/dl decline in hemoglobin or involved critical organs.

Splanchnic venous thrombosis (SVT) (Anytime) *n* (%) 38 (5) At or prior to diagnosis, *n* = 2	Other venous thrombosis (VT)[a] (Anytime) *n* (%) 77 (11) At or prior to diagnosis, *n* = 40	*p*-value univariate/ multivariate VT vs. No VT	*p*-value univariate/ multivariate CVT vs. Other VT	*p*-value univariate/ multivariate SVT vs. Other VT	*p*-value univariate/ multivariate CVT vs. SVT
40 (18–88)	67 (28–89)	.6	**<.0001/.02**	**<.0001/.0001**	.8
13 (34)	47 (61)	.8	**.0002/.05**	**.006/.03**	.09
22 (58)	49 (64)	.6	.6	.5	.9
13.1 (9–16.1)	13.8 (11.1–16)	**.02**/.07	.8	**.01**/.17	.5
10 (4–32)	9 (4–27)	.09	**.001**/.44	.2	**.0008**/.14
11/35 (31)	16/77 (21)	.9	**.02**/.44	.2	**.004/.02**
724 (230–3330)	789 (457–2869)	.6	**.002/.0003**	.8	**.03/.01**
18/38 (47)	54/76 (71)	.5	**<.0001/.02**	**.01**/.34	**.001**/.09
3/38 (8)	9/76 (12)	.9	**.05**/.14	.5	.13
8/38 (21)	44/76 (58)	.9	**<.0001/.01**	**.0001**/.17	.15
13/38 (34)	23/76 (30)	.2	**.001/.02**	.7	**.001/.01**
n = 38	*n* = 77				
31 (82)	53 (69)	**.003/.01**	.6	.1	.1
3 (7)	18 (23)	**.005/.05**	.09	**.03/.03**	.8
0	1 (1)	.4	.7	.3	–
4 (11)	5 (6)	.3	.3	.3	.6
n = 7	*n* = 30				
0	1	.9	.8	.5	–
0	1	.9	.8	.5	–
0	0	.4	–	–	–
1	2	.4	.7	.5	.6
0	0	.3	–	–	–
1	0	.4	–	.06	.6
0	1	.6	.8	.5	–
0	1	**.05/.03**	.8	.5	–
1	1	.7	.8	.3	.6
1	6	**.03/.03**	.5	.7	.6
0	0	.4	–	–	–
0	0	.4	–	–	-
1/35 (3)	2/61 (3)	–	.3	.8	.3
1/35 (3)	0	–	–	–	–
0	0	–	–	–	–
0	2/61 (3)	–	–	–	–
n = 38	*n* = 77				
2 (5)	10 (13)	**<.0001**	.1	.5	.4
5 (13)	6 (8)				
1 (3)	3 (4)				
30 (79)	58 (75)				
3 (9)	19 (25)	**.05/.01**	.3	**.02**/.41	.6
5 (13)	21 (27)	**.04**/.63	**.04**/.27	.07	.4
9/37 (24)	6/75 (8)	**.0002/.0001**	.6	**.02/.03**	.3
10/37 (27)	18/75 (24)	**<.0001/.0003**	.08	.7	.06

direct oral anticoagulants in 20 (21%), enoxaparin in 9 (9%), heparin in 4 (4%), and fondaparinux in 1 (1%) of cases. Cytoreductive therapies included hydroxyurea in 47 (49%) and anagrelide in 7 (7%) patients.

At a median follow-up of 8.7 years (range: 1–49.4 years), subsequent venous thrombosis was documented in 64 (9%; 1 per 100 patient-years) with recurrent events in 16 of 83 (19%; 2.2 per 100 patient-years) with prior venous thrombosis. Recurrence rates were highest with SVT (32%, $n = 9$) followed by other VT (15%, $n = 6$), and CVT (7%, $n = 1$) ($p < .0001$; Figure 1A). Provoked ($n = 22$) versus unprovoked ($n = 61$) venous event did not impact recurrence (23% and 18%, $p = .27$); results were similar when events were site-stratified. On univariate analysis of predictors of subsequent venous thrombosis, SVT ($p < .0001$, hazard ratio [HR] 4.3), age > 60 years ($p = .01$, HR 1.9), and *JAK2* mutation ($p = .01$, HR 1.9) emerged significant, while gender differences were not significant ($p = .10$); SVT and age > 60 years retained significance on multivariable analysis. In patients with SVT, recurrent events included SVT ($n = 6$, 66%), pulmonary embolism ($n = 1$, 10%), deep vein thrombosis ($n = 1$, 10%), and CVT ($n = 1$, 10%); four patients were already on systemic anticoagulation at the time of recurrence ($n = 2$ anticoagulation alone, $n = 1$ anticoagulation plus aspirin, $n = 1$ anticoagulation plus cytoreductive therapy), and three on cytoreductive therapy. Overall, recurrence occurred in 10/47 (21%) patients receiving systemic anticoagulation, 0/4 (0%) patients receiving cytoreduction alone, 3/16 (19%) patients receiving systemic anticoagulation plus cytoreduction, and 3/16 (19%) patients with neither anticoagulation nor cytoreduction ($p = .60$). Blood counts at the time of recurrent VT were available in nine patients, of which platelet count was below 450×10^9/L, $450–600 \times 10^9$/L and above 1000×10^9/L in three, four, and two patients, respectively.

Incidence rates for major hemorrhage were higher among patients with SVT (27%) and other VT (24%) compared to those with CVT (6%; $p = .06$ and $p = .08$, respectively). Moreover, major hemorrhage was more likely to occur with anticoagulation plus aspirin (33%) versus anticoagulation alone (21%; $p = .06$). Neither history of venous thrombosis nor site of event impacted overall survival, fibrotic and leukemic transformation, or arterial thrombosis; the superior overall survival and lower incidence of arterial thrombosis observed in patients with SVT was fully accounted for by differences in age (Figure 1B–E).

The management of MPN-associated venous thrombosis continues to be an unmet clinical need. Prior studies are limited by the retrospective design, combining arterial and venous events and inclusion of all MPN subtypes.[9] However, given the differential risk of venous thrombosis among patients with ET, polycythemia vera (PV), and primary myelofibrosis (PMF), interpretation and extrapolation of results from the former studies poses a major challenge. The current study is the foremost to report on site-specific major venous thrombosis in ET patients fulfilling the WHO 2016 diagnostic criteria, thus excluding cases with pre-fibrotic myelofibrosis. Our study provides overall and site-specific incidence and recurrence rates for major venous thrombosis, and illustrates phenotypic and genotypic distinctions, confirming the association of CVT and SVT with younger age

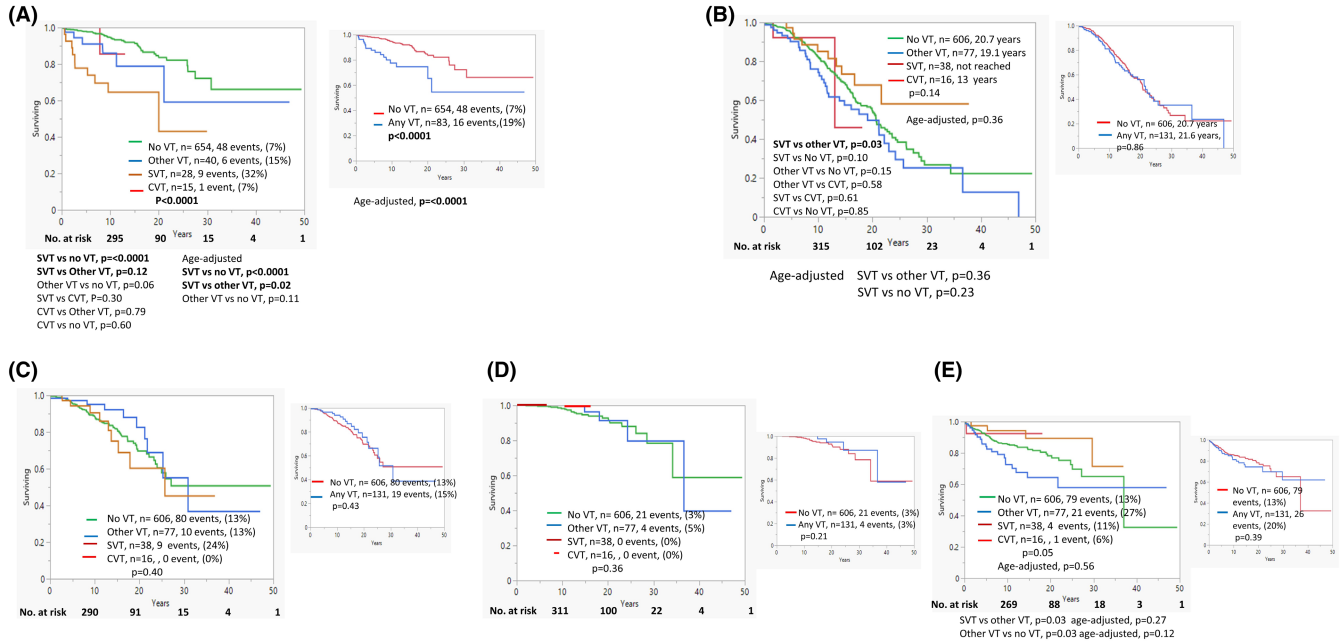

FIGURE 1 A, Venous thrombosis–free survival of 737 patients with essential thrombocythemia stratified by absence/presence and site of venous thrombosis prior to or at diagnosis. B, Overall survival of 737 patients with essential thrombocythemia stratified by absence/presence and site of venous thrombosis any time. C, Myelofibrosis-free survival of 737 patients with essential thrombocythemia stratified by absence/presence and site of venous thrombosis any time. D, Leukemia-free survival of 737 patients with essential thrombocythemia stratified by absence/presence and site of venous thrombosis any time. E, Arterial thrombosis-free survival of 737 patients with essential thrombocythemia stratified by absence/presence and site of venous thrombosis any time. CVT, cerebral venous thrombosis; SVT, splanchnic venous thrombosis; VT, venous thrombosis.

and *JAK2*V617F mutation.[6,7] Moreover, patients with VT, compared to those without VT, were more likely to harbor *TET2* and *SH2B3* mutations. Noteworthy observations include a high rate of recurrent venous thrombosis; risk was heightened five- and two-fold with SVT, in relation to those without venous thrombosis or other VT, respectively. Importantly, despite high recurrence rates, major venous thrombosis did not adversely impact overall survival, in contrast to PV.[10] Taken together, our findings reinforce the need to consider site of venous thrombosis in prognostic risk assessment in ET.

AUTHOR CONTRIBUTIONS

NG and AT designed the study, collected data, performed analysis, and co-wrote the paper. AS and NS collected data and performed analysis. CAH performed review of bone marrow biopsies. KB, ME, APW, and AP contributed patients. VDS, AMV, and TB provided critical input. All authors reviewed and approved the final draft of the paper.

KEYWORDS

JAK2, myeloproliferative, thrombosis

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

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