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RESEARCH ARTICLE

Splanchnic vein thromboses associated with myeloproliferative neoplasms: An international, retrospective study on 518 cases

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Abstract

Myeloproliferative Neoplasms (MPN) course can be complicated by thrombosis involving unusual sites as the splanchnic veins (SVT). Their management is challenging, given

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their composite vascular risk. We performed a retrospective, cohort study in the framework of the International Working Group for MPN Research and Treatment (IWG-MRT), and AIRC-Gruppo Italiano Malattie Mieloproliferative (AGIMM). A total of 518 MPN-SVT cases were collected and compared with 1628 unselected, control MPN population, matched for disease subtype. Those with MPN-SVT were younger (median 44 years) and enriched in females compared to controls; PV (37.1%) and ET (34.4%) were the most frequent diagnoses. *JAK2*V617F mutation was highly prevalent (90.2%), and 38.6% of cases had an additional hypercoagulable disorder. SVT recurrence rate was 1.6 per 100 patient-years. Vitamin K-antagonists (VKA) halved the incidence of recurrence (OR 0.48), unlike cytoreduction (OR 0.96), and were not associated with overall or gastrointestinal bleeding in multivariable analysis. Esophageal varices were the only independent predictor for major bleeding (OR 17.4). Among MPN-SVT, risk of subsequent vascular events was skewed towards venous thromboses compared to controls. However, MPN-SVT clinical course was overall benign: SVT were enriched in PMF with lower IPSS, resulting in significantly longer survival than controls; survival was not affected in PV and slightly reduced in ET. MPN-U with SVT (n = 55) showed a particularly indolent phenotype, with no signs of disease evolution. In the to-date largest, contemporary cohort of MPN-SVT, VKA were confirmed effective in preventing recurrence, unlike cytoreduction, and safe; the major risk factor for bleeding was esophageal varices that therefore represent a major therapeutic target.

1 | INTRODUCTION

Philadelphia negative myeloproliferative neoplasms (MPN) include polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF), the latter being distinguished, according to the latest release of the World Health Organization (WHO) classification, into pre-fibrotic (prePMF) and overt PMF.[1] A minority of MPN fall into a category of MPN-unclassified (MPN-U), since they do not satisfactorily fulfill histopathologic criteria for one of the above categories. Myeloproliferative neoplasms are characterized by a definite risk of disease evolution, towards secondary myelofibrosis and acute leukemia, and show an increased risk of arterial and venous thrombosis. MPN-associated venous thromboses are not limited to usual sites, such as deep vein thrombosis and pulmonary embolism, but may typically involve unusual sites including cerebral veins (CVT) and splanchnic vessels (SVT).[2-4] SVT includes Budd-Chiari syndrome (BCS), portal vein thrombosis (PT) and other thrombotic events that occur either in isolated or multiple vessels of the portal venous axis, most commonly in the splenic (ST) and mesenteric ones (MT).[5] Myeloproliferative neoplasms are, indeed, one of the leading causes of BCS and non-malignant, non-cirrhotic PT, with a reported prevalence of 30%-50% and 15%-30%, respectively.[3,6] However, recognition of an underlying MPN can be challenging[7] since portal hypertension, iron deficiency and/or hepatic ischemia may influence hematological parameters or inappropriately increase endogenous erythropoietin.[8] *JAK2*V617F mutation is a reliable marker of underlying MPN, being found in the vast majority (76%-93%) of SVT in patients with overt MPN,[6,9-11] as well as in 25%-43% of unselected SVT.[12,13] As such, *JAK2*V617F screening is recommended for any SVT patient, to identify those MPN (15%-17%) that would otherwise be missed.[12,14] Most of them either fall in the MPN-U category[15,16] or show an isolated *JAK2* mutation[17] not associated with a clear hematologic phenotype, consistent with the hypothesis that SVT may be an early manifestation of disease.

Clinical features and outcome of MPN patients with SVT (MPN-SVT) have been reported in a number of studies, either monocentric series of consecutive cases[9,10,18,19] or larger cooperative cohorts,[11] with overall consistent findings regarding demographics and phenotype. In fact, SVT are known to occur more commonly in younger MPN patients, especially women; PV is the most frequent diagnosis; concomitant thrombophilia is reported in nearly a third of cases. MPN-SVT have a well-recognized risk of thrombotic recurrence, notwithstanding that the majority of patients are treated with long-term anticoagulation and cytoreduction. However, due to the rarity of the disease and the several unmet clinical needs regarding its management,[20] a more in-depth analysis is needed, to precisely estimate risk of recurrence and evolution of the underlying MPN, and to test how effective the current therapeutic strategies are in reducing the associated vascular risk.

2 | METHODS

MPN patients included in this study were diagnosed up to 2014, so that diagnoses were originally made according to the 2008 WHO classification;[21] for the purpose of this study, all cases were locally revised

according to WHO-2017.[1] Post-PV and post-ET myelofibrosis (PPV-MF and PET-MF, respectively) were defined according to the International Working Group for MPN Research and Treatment (IWG-MRT) criteria.[22] This study was conducted in the framework of a cooperative Italian group (AGIMM, AIRC-Gruppo Italiano Malattie Mieloproliferative) and the IWG-MRT (see Table S1 for a complete list of participating centers). After approval by the institutional review board (IRB) of the coordinating center (May 17, 2011, n 37/11, prot. 2011/18054) and local IRBs, we collected clinical, laboratory and biological data, information on treatment, major vascular events, including SVT recurrences, disease evolution and survival of 518 MPN-SVT and of 1628 MPN, used as controls. The latter were an unselected population, except for the exclusion of SVT, represented by consecutively referred patients, in the same lapse of time as SVT ones, matched with population under study only for the MPN subtype. Half of the participating centres were asked to provide at least three, and up to four controls for each MPN-SVT patient included, except for MPN-U (final ratio was 3.5 controls for every MPN-SVT case).

2.1 | Statistics

Continuous variables were summarized as median and minimum-maximum ranges. Differences among frequencies were estimated with Fisher's exact test. Wilcoxon rank-sum (Mann-Whitney) and Kruskal-Wallis equality-of-populations rank tests were used for comparisons of median values among two groups or more groups, respectively. Events of interest were SVT recurrence, venous thrombosis other than SVT, arterial thrombosis, major bleeding, evolution to secondary myelofibrosis or acute leukemia; they were expressed as event per patient-years. Recurrence of SVT as a function of time was estimated using the Kaplan-Meier method, analyzing the interval between SVT index event and date of recurrent events (uncensored observations), death or last follow up (censored observations). Incidence of other major vascular events or disease evolution as a function of time was also estimated using the Kaplan-Meier method, analyzing the interval between date of MPN diagnosis and date of subsequent event of interest (uncensored observations), death or last follow up (censored observations). Log-rank test was used for comparing survival distributions. A multivariable model was built to identify predictors of SVT recurrence-including gender, treatment with vitamin K-antagonists (VKA), cytoreduction and coexistent thrombophilia -, and predictors of major bleeding-including gender, age at SVT, treatment with heparin, VKA, antiplatelet agents, presence of esophageal varices (EV) and site of index SVT (BCS and/or PT, or isolated mesenteric/splenic vein thrombosis)-. The level of significance was set at 5%. Analyses were performed using Stata version 14 (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Patients characteristics

Among 518 MPN-SVT, PT occurred in 67.4% of the patients (n = 349), splenic thrombosis (ST) in 29.3% (n = 152), mesenteric vein thrombosis (MT) in 24.3% (n = 126) and BCS in 24.9% (n = 129). In 153 patients (29.5%) an association of PT and/or ST and/or MV was found, while an association of BCS with PT and/or ST and/or MT was found in a minority (n = 9, 1.7%). Clinical and laboratory findings of study patients' population are summarized in Table 1, except for five patients with secondary MF, whose data are not reported in detail.

In 240/509 cases (47.1%) MPN and SVT diagnosis were coincident (plus/minus 3 months), in 117 patients (23%) an SVT index event preceded MPN diagnosis of a median of 28 months (range 4-103), and in 152 (29.9%) it occurred after a median of 67 months from the diagnosis of MPN (range 4-362). BCS was prevalent in the first group, i.e. when MPN and SVT were coincident (54.7% of all BCS; 14.1% and 31.2% were diagnosed before or during MPN follow up, respectively, $P = .014$).

Among those 152 SVT index events occurring more than 3 months after MPN diagnosis, 13 (8.5%) occurred within 6 months of undergoing therapeutic or post traumatic splenectomy, while none occurred in patients treated with hormonal contraceptives or hormonal replacement therapy.

Median follow-up for the MPN-SVT cohort was 89.9 months (range 0.5-430) and 70.1 months (range 0.5-425) for control group.

PV was the most frequent MPN-SVT subtype (37.1%, n = 192), followed by ET (34.4%, n = 178), overt PMF (13.1%, n = 68), MPN-U (10.6%, n = 55), prePMF (3.9%, n = 20), PPV-MF (n = 4) and PET-MF (n = 1).

Thirty-one out of 128 PV-SVT (24.2%) were primarily diagnosed based on bone marrow findings; 21 of them (67.7%) had palpable splenomegaly (range: 2-16 cm); 10 (32.2%) had hepatomegaly (range: 2-6 cm); 9 (29%) experienced Budd-Chiari syndrome as an index event, synchronous with MPN diagnosis.

Twenty out of 132 ET-SVT (15.1%) were primarily diagnosed based on bone marrow findings; 11 of them (55%) had splenomegaly (range: 2-22 cm); seven (35%) had hepatomegaly (range: 2-4 cm); four (20%) experienced Budd-Chiari syndrome as index event, with MPN diagnosed synchronously.

Control population included 671 PV (41.2%), 697 ET (42.8%) and 260 PMF (16%), 158 were overt PMF (9.7%) and 102 were prePMF (6.3%).

Female patients were prevalent among MPN-SVT compared to controls, across all disease subtypes: 53.1% vs 41.1% in PV ($P = .004$), 58.8% vs 29.7% in overt-PMF ($P < .001$), 75% vs 28.4%, in pre-PMF ($P < .001$) and to a lesser extent in ET (71.3% vs 63.1%, $P = .043$). Females were as many as 70.9% of MPN-U patients.

Median age at MPN diagnosis was significantly lower in MPN-SVT (43.6 years, range 12-90) compared with controls (60.6 years, range 12-93) ($P < .001$); this was consistent across all MPN subtypes ($P < .001$, each). Median age at the time of SVT index event was 44 years (range 12-90); ET patients were the youngest (median age, 39 years, range 12-90, $P = .001$).

Splenomegaly was more common in MPN-SVT both for PV (56.3% vs 41.1%, $P = .002$) and ET (46.9% vs 17%, $P < .001$), while its frequency was similar in overt ($P = .095$) and prePMF ($P = .71$), irrespective of SVT.

TABLE 1 Clinical and laboratory findings of SVT and control population

		PV			ET			overt PMF			U-MPN With SVT	prePMF		
		With SVT	Without SVT	*P*	With SVT	Without SVT	*P*	With SVT	Without SVT	*P*		With SVT	Without SVT	*P*
Diagnosis	n	192/518[a]	671/1628		178/518[a]	697/1628		68/518[a]	158/1628		55/518[a]	20/518[a]	102/1628	
	%	37.1	41.2		34.4	42.8		13.1	9.7		10.6	3.9	6.3	
Gender (female)	n	102/192	276/671	**.004**	127/178	440/697	**.043**	40/68	47/158	**<.0001**	39/55	15/20	29/102	**<.0001**
	%	53.1	41.1		71.3	63.1		58.8	29.7		70.9	75.0	28.4	
Age[e], years	median	45	61	**<.0001**	39	57	**<.0001**	46	65	**<.0001**	46	48	68	**<.0001**
	range	15-75	17-93		12–90	13-92		25-78	18-90		17-74	22-70	28-89	
Evolution to PPV/PET-MF	n	29/192	80/671	.27	20/178	69/697	.58							
	%	15.1	11.9		11.2	9.9								
Evolution to AL	n	6/184	6/351	.36	5/160	9/469	.36	2/68	22/141	**.005**	0/55	0/20	14/88	.068
	%	3.3	1.7		3.1	1.9		2.9	15.6		0	0	15.9	
Age at SVT diagnosis, years	median	45			39			46			46	48		
	range	15–75			12–90			25–78			17–74	22–70		
Death	n	36/191	54/541	**.002**	25/178	25/468	**<.0001**	14/68	78/154	**<.0001**	1/55	3/20	44/102	**.023**
	%	18.8	10.0		14.0	5.3		20.6	50.6		1.8	15.0	43.1	
*JAK2*V617F mutation	n	143/148	597/640	.18	126/148	407/672	**<.0001**	44/52	92/141	**.012**	45/48	17/20	61/82	.39
	%	96.6	93.3		85.1	60.6		84.6	65.2		93.7	85	74.4	
*JAK2*V617F allele burden, %	median	47.7	45	.63	29.5	22	**.0029**	30	41	.47	19.2	43	39	.30
	range	4.8-100	1-100		1–100	1-87		9-89	1–100		1-48	11-87	1-86	
Abnormal karyotype	n	12/84	27/235	.56	5/79	8/239	.32	4/22	33/85	.058[b]	1/24	1/12	14/62	
	%	14.3	11.5		6.3	3.3		18.2	38.8		4.2	8.3	22.6	
Coexistent hypercoagulable disorder[c]	n	47/121	32/362	**<.0001**	37/110	44/329	**<.0001**	16/41	5/12	1.0	19/42	7/14	2/2	.47
	%	38.8	8.8		33.6	13.4		39	41.7		45.2	50	100	
Hemoglobin (g/dL)[e]	median	17	18.1	**<.0001**	13.9	14.1	.10	11.4	11	.41	13.6	12.4	12	.30
	range	8.6–23	14.7-24.5		7.8-18.4	9.6-17		5.6-20	5-16.4		10.8-15.6	8.3-16.3	5.3-18.3	
White blood cells (WBC, $\times 10^9$/L)[e]	median	10.1	10	.88	9.7	8.4	**<.0001**	6.4	9.5	**.016**	7.1	7.9	10.5	**.018**
	range	1.8-36.5	4.3-125		4-38.2	3.2-18.3		3-69.5	1.4-90.8		4.1-16	4.8-9.1	0.7-108	
Platelet count (PLT, $\times 10^9$/L)[e]	median	409	443	**.047**	691	714	.068	229	266	.87	303	426	416	.66
	range	28-1500	51-1352		81-3300	402-2348		76-2011	19-1392		145-632	181-827	2-1246	
LDH (U/L)[e]	median	335	313	.74	295	286	.64	400	700	**<.0001**	311	294	466	.053
	range	78-957	123-1762		110-1075	102-783		113-1022	130-2981		161-3059	201-1650	146-2643	
Constitutional symptoms[e]	n	17/134	79/504	.42	6/115	13/412	.27	17/45	65/150	.61	2/25	3/12	34/102	.75
	%	12.7	15.7		5.2	3.16		37.8	43.3		8	25	33.3	
Splenomegaly[e]	n	76/135	254/618	**.002**	53/113	108/635	**<.0001**	38/46	135/147	.095	17/25	10/13	80/98	.71
	%	56.3	41.1		46.9	17		82.6	91.8		68	76.9	81.6	
Oesophageal varices	n	100/166			104/154			44/61			43/53	13/20		

(Continues)

TABLE 1 (Continued)

		PV			ET			overt PMF			U-MPN	prePMF	
		With SVT	Without SVT	*P*	With SVT	Without SVT	*P*	With SVT	Without SVT	*P*	With SVT	With SVT	Without SVT
	%	60.2			67.5			72.1			81.1	65	
Bleeding events	n	57/192	42/671	**<.0001**	60/178	49/697	**<.0001**	31/88[c]	25/260[d]	**<.0001**	16/55		
	%	29.7	6.3		33.7	7		35.2	9.6		29.1		
Bleeding events, excluding varicéal ones	n	20/192	42/671	**.049**	22/178	49/697	**.020**	8/88	25/260[d]	.88	3/55		
	%	10.4	6.3		12.4	7		9.1	9.6		5.4		

[a]MPN-SVT cohort includes 5 more patients with secondary myelofibrosis, up to a total of 518 cases.
[b]*P* value refers to the whole cohort of PMF. Abnormal karyotype in the SVT-PMF group included 20q deletion, 5q deletion, trisomy of chromosome 9 and 8. According to the most recent classification of cytogenetic abnormalities,[23] 2 out of 5 SVT-PMF cases had an unfavorable karyotype, while among PMF controls there were 18 unfavorable and 8 very high risk karyotypes out of 47 informative cases.
[c]Included antithrombin, protein C and protein S levels, factor V Leiden and/or activated protein C (APC) resistance, prothrombin gene G20210A mutation, hyper-homocysteinemia, lupus anti-coagulant (LAC), anticardiolipin and anti-beta2-glycoprotein antibodies. Use of hormonal contraception (HC) or replacement therapy (HRT) was recorded, but it was not analyzed separately due to low patients' number (n = 2).
[d]Data refer to the whole cohort of PMF.
[e]Refers to the time of MPN diagnosis.

Active smoking and hyperlipidaemia were equally distributed between MPN-SVT and controls (17.1% vs 17.0%, *P* = .96, and 7.7% vs 10.7%; *P* = .14, respectively), while diabetes and hypertension were less common in MPN-SVT (5.4% vs 8.9%, *P* = .043; 15.7% vs 45.8%, *P* < .001, respectively), possibly due to the younger age of the MPN-SVT cohort.

3.2 | Hematological parameters

At MPN diagnosis, compared to their control counterpart, PV-SVT patients had lower platelet counts (*P* = .047) and hemoglobin (*P* < .001), both in males (17.4 g/dL, range 8.6-23, vs 18.5 g/dL, range 15-24.5, *P* < .001) and females (17 g/dL, range 10.5-22, vs 17.7 g/dL, range 14.7-22.8, *P* = .006); white blood cell counts were higher in ET-SVT (*P* < .001), and lower in both overt PMF and prePMF with SVT (*P* = .016 and *P* = .018, respectively); other blood counts were otherwise comparable (Table 1).

Hematological parameters at the time of SVT index events are summarized in Table 2.

Both PV and ET patients showed significantly lower hemoglobin compared to their diagnostic baseline (*P* < .001 and *P* = .0052, respectively); ET cases had lower platelet counts (*P* < .0001) and showed a trend towards higher leukocyte counts (*P* = .057); conversely, overt and prePMF patients showed comparable values.

3.3 | Molecular features

*JAK2*V617F mutation was found in 90.2% (379/420) of SVT cases, five (1%) had a *CALR* type I mutation and three (0.6%) had a *MPL*W515K mutation.

Frequency of *JAK2*V617F was significantly higher in ET and PMF with SVT compared to their control counterpart (85.1% vs 60.6% in ET, *P* < .001; 84.6% vs 65.2% in PMF, *P* = .012), while it was similar in PV irrespective of SVT, as expected. 93.7% (45/48) of MPN-U cases were *JAK2*V617F mutated.

Median *JAK2* allele burden was higher in ET-SVT compared with ET controls (29.5% vs 22%, *P* = .029).

There was a trend towards fewer abnormal karyotypes in the overall group of SVT-PMF patients (overt plus prePMF) (5/34, 15%) compared with PMF controls (47/147, 32%) (*P* = .058). See Table 1 for details regarding frequency of unfavorable and very high risk karyotypes.[23]

3.4 | Hypercoagulable disorders

Information regarding hypercoagulable disorders was available in 329 (63.5%) MPN-SVT and 705 (43.3%) controls; more than one third of MPN-SVT cases (38.6%) showed at least one co-existing risk factor (127/329) vs 11.8% of controls (83/705) (*P* < .001). In particular, a highly significant difference was shown among PV and ET, with or without SVT (*P* < .001 each); informative cases among PMF were unfortunately limited.

TABLE 2 Complete blood cell counts at MPN and SVT diagnosis

		PV			ET			Overt PMF			PrePMF		
		At MPN diagnosis	At SVT diagnosis	*P*	At MPN diagnosis	At SVT diagnosis	*P*	At MPN diagnosis	At SVT diagnosis	*P*	At MPN diagnosis	At SVT diagnosis	*P*
HB, g/dl	median	17	14.3	**<.0001**	13.9	13.2	**.0052**	11.4	11.1	.20	12.4	14	.32
	range	8.6-23	7.4-19.2		7.8-18.4	6-17.3		5.6-20	4.8-15.9		8.3-16.3	10.8-15.5	
WBC, $\times 10^9$/L	median	10.1	11.3	.094	9.7	10.3	.057	6.4	9.2	.96	7.9	8	.32
	range	1.8–36.5	2.2-68.3		4-38.2	2.2-27.1		3-69.5	1.5-128		4.8-9.1	7-9	
PLT, $\times 10^9$/L	median	409	379	.088	691	497	**<.0001**	229	342	.88	426	374	.32
	range	28–1500	26-2721		81–3300	4.8-3300		76-2011	6-1360		181-827	189-827	

3.5 | Therapy

Most of the SVT index events (85%) developed in the absence of any antithrombotic prophylaxis. Conversely, the majority of patients (91.6%, 447/488) received anticoagulants and/or antiplatelet agents for secondary prophylaxis. In detail, anticoagulants were administered to 84.6% of patients (heparin in 34% and VKA in 66% of cases), antiplatelet agents in 11.8% (either aspirin or ticlopidine or clopidogrel) and a combination of the former in 3.6%.

First choice of therapy was modified in nearly a third of patients (138/453, 30.5%); in the 58/138 informative cases, reasons for change were hemorrhages in 20 (mostly variceal bleeding and a single case of cerebral hemorrhage), recurrence of SVT or other venous thromboses in 18, arterial events in four (including two acute myocardial infarctions and a stroke), and other reasons in 14, including management of pregnancy or major surgery.

Cytoreductive agents were used in 70.4% of the cases (360 of 511 for whom information was available), mostly hydroxyurea (85% of cases); other treatments included anagrelide (n = 32), interferon (n = 51), and ruxolitinib (n = 20). Four patients (one PMF, two PET-MF, one PPV-MF) received an allogeneic transplantation and two BCS cases underwent orthotopic liver transplant. Transjugular intrahepatic portosystemic shunt (TIPSS) procedure was performed in 12.5% of patients to reduce portal hypertension while beta blockers were used in 46.4% of patients.

3.6 | Risk of recurrence and vascular events

Incidence rates of major vascular events, expressed as number of events per 100 patient-years, are summarized in Table 3.

A total of 62 patients (out of 516 informative cases, 12%) experienced SVT recurrence, that involved more than one site in 18 cases (29%); isolated recurrences were PT in 15 cases, MT in 10, BCS in 11, ST in three, and TIPSS thrombosis in four (one site of recurrence was unknown). Incidence rate of recurrence was 1.6 (95% CI 1.2-2.1), and there was a significant difference in recurrence on and off VKA (1.1, 95% CI 0.7-1.7, vs 2.3, 95% CI 1.6-3.2, P = .013).

Logistic regression analysis of therapy-related factors (VKA and cytoreduction), gender and coexistent thrombophilia confirmed a single, inverse association of SVT recurrence and use of VKA (OR 0.48, 95% CI 0.24-0.95, P = .034), while cytoreductive therapy had an OR of 0.96 (95% CI 0.47-1.95, P = .91). A larger multivariable model, that included diagnostic features as MPN subtype and *JAK2*V617F mutation, did not disclose any additional significant association.

Incidence rate of venous thrombosis other than SVT was significantly higher in MPN-SVT compared to controls (1.6, 95% CI 1.3-2.0, and 0.7, 95% CI 0.5-0.9, P < .001); this observation was quite consistent across all MPN subtypes, except for PV (see Table 3 for details).

Conversely, incidence rate of arterial thrombosis was higher among controls (3.0, 95% 2.6-3.3) compared to MPN-SVT (1.6, 95% CI 1.2-2.0) (P < .001), consistently across MPN subtypes, except for

PMF. Treatment with VKA did not affect the risk of subsequent arterial events (data not shown in detail).

Overall, 67% of MPN-SVT patients (307/458) presented with or developed EV, and 44.5% of them experienced one or more episodes of bleeding from varices (range 1-6); no significant difference was found between frequency of EV across MPN subtypes, nor there was any correlation with splenomegaly, either at the time of MPN diagnosis or at SVT index event.

Major hemorrhages were more frequent in MPN-SVT compared with control population without SVT ($P < .001$ for each diagnosis; see Table 1 for details), but were mainly related to EV. In fact, excluding bleedings from varices, incidence rate of hemorrhage was 1.2 (95% CI 0.9-1.6) among MPN-SVT and 1.0 (95% CI 0.8-1.2) among controls. Frequency of hemorrhage was similar in the overall PMF group with and without SVT ($P = .88$), slightly increased in PV with SVT ($P = .049$), and significantly increased in ET with SVT ($P = .020$). Frequency of bleeding among MPN-U with SVT was comparable with the rest of MPN-SVT cohort (see Table 1 for details).

Logistic regression analysis of gender, age at SVT, therapy-related factors (heparin, VKA, antiplatelet agents), EV and site of index SVT (BCS and/or PT, or isolated MT or ST) revealed a single positive association of EV and major bleeding (OR 17.4, 95% CI 8.1-37.4, $P < .0001$); this association was even more pronounced when the model was tested to identify predictors of gastrointestinal bleeding (OR 94.7, 95% CI 13.0-691.9, $P < .001$). Unfortunately, information on whether cytoreduction was ongoing at the time of bleeding was not available; so, it was not considered as a reliable covariate to be tested.

3.7 | Disease evolution and Survival

No differences were found in the rate of evolution to acute leukemia (AL) for PV and ET patients with or without SVT ($P = .36$ and $P = 0.49$, respectively); rate of evolution to secondary myelofibrosis was comparable for ET-SVT ($P = .20$) and lower in PV-SVT ($P = .034$) compared to controls. Of note, overt PMF-SVT had lower incidence of AL compared to those without SVT ($P = .005$), and no patients with prePMF evolved to AL in the SVT cohort (see Table 3 for details). No disease evolution occurred among MPN-U.

At last follow up, 80/516 pts (15.5%) with MPN-SVT had died; causes of death are summarized in Table S2.

Median overall survival (OS) was similar in PV with and without SVT (24.9 vs 23.8 years, respectively, $P = .76$), and shorter in ET with SVT vs ET controls ($P < .001$), although median survival in both groups was well above 30 years (Figure 1A,B). Conversely, median OS of PMF-SVT patients was significantly longer compared with control population, both for overt (22.1 vs 6.1 years; $P < .001$), and prePMF (not reached vs 7.1 years, $P = .013$) (Figure 1C, D). This finding was mirrored by a higher proportion of SVT patients in lower IPSS risk categories ($P < .001$) (Table S3). However, we acknowledge that survival estimates for prePMF patients were affected by right censoring (median follow-up: 6.9 years).

A stratified log-rank test, according to *JAK2* mutational status, showed that OS was not statistically different between ET-SVT and *JAK2*V617F-positive ET-controls ($P = .73$). Similar results were obtained considering *JAK2*V617F-positive ET and PV as a single group, with or without SVT ($P = .92$).

TABLE 3 Incidence rates of major vascular events and disease evolution, expressed as number of events per 100 patient-years

	MPN-SVT	*P*	MPN control population	*P*
SVT recurrence, overall	1.6 (95% CI 1.2-2.1)			
- on VKA	1.1 (95% CI 0.7-1.7)	**.013**		
- off VKA	2.3 (95% CI 1.6–3.2)			
Venous thromboses other than SVT	1.6 (95% CI 1.3–2.0)		0.7 (95% CI 0.5–0.9)	**<.0001**
- PV	1.3 (95% CI 0.9-2.0)		0.7 (95% CI 0.5-1.1)	.14
- ET	1.4 (95% CI 0.9-2.1)		0.5 (95% CI 0.3-0.7)	**.0029**
- PMF	2.7 (95% CI 1.6-4.4)		1.1 (95% CI 0.7-1.9)	**.040**
Arterial thromboses	1.6 (95% CI 1.2–2.0)		3.0 (95% 2.6-3.3)	**<.0001**
- PV	1.5 (95% CI 1.0-2.2)		3.6 (95% CI 3.0-4.3)	**<0.0001**
- ET	1.3 (95% CI 0.9–2.0)		2.4 (95% CI 2.0-2.8)	**.0038**
- PMF	2.6 (95% CI 1.6–4.4)		3.3 (95% CI 2.4-4.6)	.46
Major bleeding[a]	1.2 (95% CI 0.9-1.6)		1.0 (95% CI 0.8-1.2)	.95
Evolution to secondary myelofibrosis, PV	1.5 (95% CI 1.1-2.3)		1.7 (95% CI 1.4-2.2)	**.034**
Evolution to secondary myelofibrosis, ET	1.2 (95% CI 0.8-1.8)		1.4 (95% CI 1.1-1.7)	.20
Evolution to acute leukemia, PV	0.3 (95% CI 0.1-0.8)		0.2 (95% CI 0.1-0.4)	.36
Evolution to acute leukemia, ET	0.3 (95% CI 0.1-0.7)		0.2 (95% CI 0.1-0.4)	.49
Evolution to acute leukemia, overt PMF	0.5 (95% CI 0.1-1.8)		3.0 (95% CI 2.0-4.5)	**.0053**
Evolution to acute leukemia, prePMF	0		3.1 (95% CI 1.8-5.4)	0.081

[a]Excluding variceal complications.

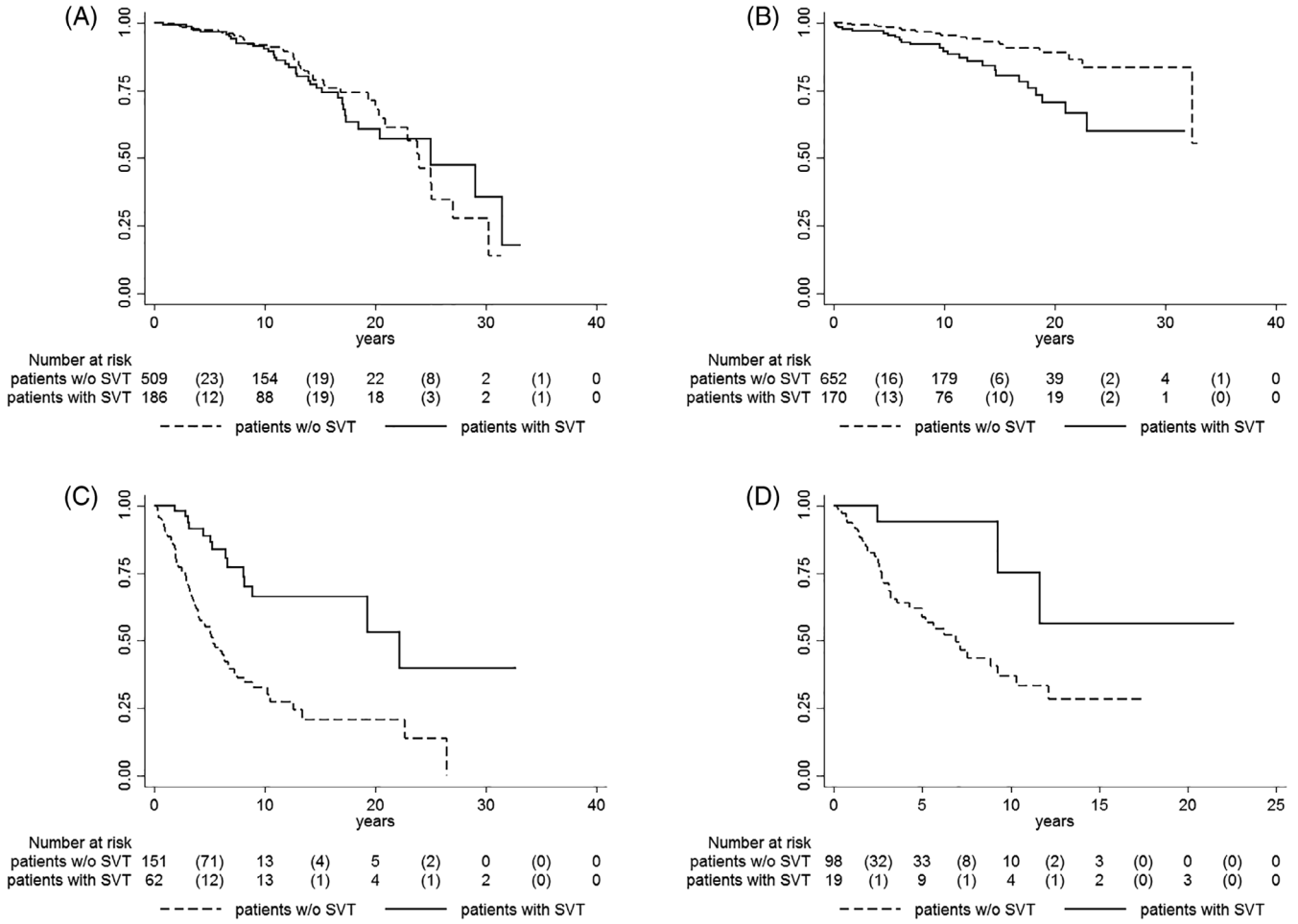

FIGURE 1 Overall survival of PV (A), ET (B), PMF (C) and prePMF (D) patients, with and without SVT. Numbers of censored patients are reported in parentheses

4 | DISCUSSION

Vascular complications are among the most common causes of morbidity and mortality of MPN patients,[24] so that medical intervention in this setting is typically directed to reduce vascular risk.[2,25] MPN-associated thromboses involve venous vessels in about one-third of cases: although the vast majority of these events occur at usual sites (deep venous thrombosis and/or pulmonary embolism), splanchnic and cerebral venous thromboses (CVT) are highly overrepresented in MPN compared with the general population.[5,26] Indeed, CVTs have an estimated annual incidence of 3-4 cases per million, but as many as 1% of MPN patients may be affected[26]; SVT incidence in the general population ranges from 0.8 per million (BCS) to 0.7 per 100 000 (PT), but their prevalence in MPN may be as high as 10%-13%.[6,27]

Management of MPN-SVT is challenging given their composite vascular risk that includes a high risk of both thrombotic recurrence and major bleeding, especially from EV. Though there is a general agreement in maintaining long-term anticoagulation, valuing the underlying hematological disorder as a permanent risk factor,[28,29] recurrent thromboses - either SVT or not - are reported in a non-trivial proportion of MPN-SVT, ranging from 16%-17%[9,11] to 27%.[18] While in the general population VKA are effective after venous thromboembolism at usual sites,[30-32] their efficacy and safety are overall less favorable in MPN patients, with higher rates of recurrences and major bleeding, particularly when dealing with thromboses at unusual sites, as SVT or CVT.[33] In a large (n = 181), contemporary cohort of MPN-SVT, rate of major bleeding was reported to be 2.1 (95% CI 1.3-3.5) per 100 patient-years,[11] which is higher than expected for non-splanchnic deep venous thromboses in the general population treated with VKA (0.9 [95% CI 0.4 to 3.0] per 100 patient-years).[34]

Moreover, the ultimate impact of SVT on MPN patients' survival remains debated.

The aim of the present study was to improve the knowledge of MPN-SVT through the analysis of a large cohort of cases (n = 518), collected in 18 international centres referring to two cooperative groups (AGIMM, IWG-MRT). We aimed at characterizing clinical and biological features of MPN-SVT, and elucidating their outcome, in terms of OS and vascular risk, compared to a reference population of MPN patients (n = 1628) without SVT. To the best of our knowledge, this is the largest series reported so far in this field, including a disease matched control group, therefore it might be regarded as the most

informative, yet with the intrinsic limitations of a retrospective series, justified by the relative rarity of the disease.

We confirmed a consistent association of SVT with a definite phenotype, characterized by prevalence of female sex and younger age (at the time of both MPN diagnosis and SVT), across all MPN subtypes, and a striking association with *JAK2*V617F mutation (90.2% in our cohort); PV and ET were the most frequent underlying diagnoses. In this regard, we acknowledge that accurate differentiation among MPN-SVT subtypes may pose a diagnostic challenge, particularly as regards ET and PV.[15] In line with this notion, as much as 20% of ET- and PV-SVT cases included in our study were primarily diagnosed based on bone marrow findings.

Sex and age distribution are different from those observed in the general population and in MPN patients without SVT, suggesting that traditional risk factors for thrombosis are of limited value in the context of MPN-SVT. Although the pathophysiological mechanisms that might explain this phenotypic association are not completely understood,[35] we may argue that some of the cooperating risk factors for MPN-SVT, as hereditary thrombophilia, pregnancy and/or use of oral contraceptives, are, indeed, more frequently encountered in younger and female subjects. At the same time, local factors, such as low shear rates in hepatic veins, *JAK2*-mutated endothelial cells and altered portal blood flow,[3] have an undisputed role in modulating disease presentation.

We found that MPN-SVT cases had a risk of subsequent vascular events that was skewed towards venous thromboses: rate of SVT recurrence and rate of venous thrombosis other than SVT were each 1.6 per 100 patient-years. Although we acknowledge the limitations of comparing data among non-homogeneous cohorts, recurrent thrombosis in our cohort was consistent with previously reported rates (4.2 per 100 patient-years), indirectly supporting our findings.[11]

Opposed to cytoreduction, VKA halves the incidence of recurrent thromboses, being a significant independent protective factor in the multivariable analysis (OR 0.48). These findings are consistent with those obtained in a multicenter cohort of MPN-related thrombosis (n = 1500), in which recurrences were significantly reduced by VKA after an index venous event, and by hydroxyurea after an index arterial thrombosis.[36] Notably, hydroxyurea was not protective in the subgroup of SVT (n = 218).[36]

Major bleeding was more frequent in MPN-SVT compared to the control population, being mainly related to variceal complications (OR 17.4); notably, in our multivariable model, VKA was not associated with increased overall or gastrointestinal bleeding. Our data agree with those recently reported by Riva et al,[37] regarding VKA safety in SVT (n = 375, 20% of whom MPN-associated); they, indeed, identified EV as an independent predictor of major bleeding, with an OR of 5.4.

According to our data, occurrence of SVT should not be regarded as a feature suggesting an underlying, aggressive MPN by itself. Rates of disease evolution to AL were overall comparable with those observed in controls, matched by MPN diagnosis, and rate of secondary myelofibrosis was lower in PV with SVT compared to controls. In the past, MPN-SVT were indeed reported as "atypical myeloproliferative disorders with high thrombotic risk and slow disease progression".[38]

Notably, our cohort of 55 MPN-U showed a very indolent clinical course, without evidence at all of hematological progression or evolution, and with excellent survival (we observed a single death, due to SVT-related complications). Similar findings were recently reported in a smaller cohort (n = 8),[9] supporting the notion that MPN-U with SVT represents a very early phase of hematological neoplasm without full blown histopathologic and hematologic features indicative of a specific disease subtype according to WHO criteria. It cannot be ruled out, however, whether these cases constitute a biologically distinct MPN subtype.

Survival of MPN-SVT patients is regarded to be primarily influenced by the natural history of the underlying neoplasm, rather than by the recurring thrombotic event and/or the consequences on splanchnic circulation and liver function. Our current findings seem to be well consistent with this hypothesis, with a notable exception. We found no difference in survival for PV patients, with or without SVT, while outcome of PMF (both overt and prePMF) in the SVT cohort was even more favorable. In the latter case, this was reflected by the prevalence of lower IPSS risk categories among PMF patients with, rather than without, SVT. On the other hand, the natural history of ET patients, whose life expectancy is known to be only mildly compromised compared to the general population, appeared to be negatively influenced by the occurrence of SVT, although median survival was estimated to be longer than 30 years irrespective of SVT.

Moreover, stratified survival analysis revealed a quite similar clinical outcome among genetically-defined subgroups; this observation is particularly intriguing in the setting of MPN-SVT, where the disease is strictly linked to *JAK2*V617F mutation and where boundaries among MPN subtypes may be elusive, as previously noted.

In conclusion, SVT in MPN, either at diagnosis or during the course of the disease, appears to be characterized by unique clinical features and outcome. A working hypothesis, that needs to be substantiated further, might be formulated, where all *JAK2*V617F-mutated MPN with SVT represent a single clinical entity, with homogenous prognosis in spite of different hematologic and clinical phenotypic expression. Results of this analysis may offer insights for future studies concerning pathobiology of the disease as well as therapeutic approach. In particular, they appear reassuring as regards the safety and efficacy of VKA, particularly in the era of new direct anticoagulants, and rather point to the opportunity of careful, proactive monitoring and management of esophageal varices.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

AMV, LP and PG designed the research and collected clinical data; MP, MLR, CS, ES, FC, FD, AC, SB, ER, NL, CH, NCG, HG, BG, GS, AR, NV, NP, MKM, MR, FG, ME, AI, FM, LM, BS, GGL were involved in patient management and collected clinical data; ES analyzed the data and wrote the manuscript; AMV and PG critically revised and finalized the manuscript; all authors discussed the results and contributed to the final paper.

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SUPPORTING INFORMATION

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