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Title: Patients with post polycythemia vera myelofibrosis might experience increased thrombotic risk in comparison to primary and post essential thrombocythemia myelofibrosis

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Dear Editor,

Primary myelofibrosis (PMF), post-polycythemia vera (post-PV) and post-essential thrombocythemia (post-ET) secondary myelofibrosis (SMF) are chronic myeloproliferative neoplasms (MPNs) characterized by bone marrow fibrosis, splenomegaly and debilitating constitutional symptoms. Despite clinical similarities, PMF and SMF harbor different mutational backgrounds [1] and optimal prognostication of risk of death is achieved utilizing specialized prognostic scores (DIPSS [2] and Mysec-PM [3], respectively). PMF and SMF patients also suffer from a substantial risk of thrombotic events that might be comparable to PV and ET patients [4], and is probably modulated by similar factors. Nevertheless, thrombotic risk in myelofibrosis patients is often overlooked and risk-factors for thrombosis are less well characterized. In this report we aimed to assess potential differences in thrombotic risk between PMF, post-PV and post-ET SMF from our multicentric cohort of patients with myelofibrosis.

We retrospectively analyzed a cohort of 248 patients with myelofibrosis from 6 Croatian hematology centers diagnosed in period from 2004-2021. Diagnoses of PMF and SMF were established according to the 2016 and 2008 criteria [5, 6]. The Kruskal-Wallis-ANOVA, the X^2 test, the log-rank test and the Cox-regression were used. All analyzes were performed using the MedCalc-statistical-software v20.109 (MedCalc-Software-Ltd,Ostend,Belgium).

Among a total of 248 analyzed patients, there were 177 PMF, 37 post-PV and 34 post-ET SMF patients. A total of 170 (72%) were JAK2 mutated patients, 152 (61.3%) were males. Median age was 68 years, IQR (60-75). Patients' characteristics stratified according to the etiology of myelofibrosis are shown in Table 1. Post-PV SMF patients the least frequently were of male sex or had cardiovascular risk factors, the most frequently had constitutional symptoms, massive splenomegaly and baseline hematocrit $\geq 45\%$, had

highest white blood cell count (WBC) and lowest absolute lymphocyte count, serum iron, uric acid and albumin in comparison to other myelofibrosis subsets. Patients with PMF the least frequently had presence of circulatory blasts, overt bone marrow fibrosis and positive history of baseline thrombosis and had lowest MCV in comparison to other myelofibrosis subsets.

Median follow-up of our cohort was 55 months. During the follow up period a total of 110 patients died, 29 patients experienced thrombosis (27 arterial and 10 venous) and 18 patients experienced bleeding. Overall survival was highest among post-ET patients in comparison to PMF and post-PV patients (overall $P=0.050$, Figure 1A). Time to arterial thrombosis was shortest in post-PV SMF patients in comparison to PMF and post-ET SMF patients who had comparable thrombotic risk (overall $P=0.014$, Figure 2B), whereas there were no significant differences regarding time to venous thrombosis and time to bleeding according to the etiology of myelofibrosis ($P>0.05$ for both analyses). Association of post-PV SMF with the risk of thrombotic events was further evaluated in the Cox regression model adjusted for clinically meaningful variables (Supplementary Table S1). Post-PV SMF remained significantly associated with shorter time to thrombosis independently of WBC, chronic kidney disease and higher estimated plasma volume status.

There are several important points we would like to emphasize. Our study is the first to report that post-PV SMF patients seem to experience highest risk of arterial thrombotic events among myelofibrosis subtypes, whereas similar risk of venous thrombotic events was observed. We also confirm previous findings that post-ET SMF patients experience most favorable overall survival [7]. Reasons for highest risk of arterial thrombotic events among post-PV SMF are unknown, especially considering that these patients had lowest frequency of classic cardiovascular risk factors. However, they most frequently had baseline hematocrit values $\geq 45\%$, JAK2 mutation, constitutional symptoms, massive splenomegaly and highest WBC, features of stronger myeloproliferation that might promote blood viscosity and accelerated

atherosclerosis. Potential contribution of iron deprivation to thrombotic risk [8] is also unknown. Considering that clinical focus shifts from thrombotic risk control to quality of life and risk of death in MPN patients developing SMF, these patients might be less frequently phlebotomized and specific therapies might be withheld in the fear of anticipated anemia and thrombocytopenia. Among investigated clinically meaningful variables, post-PV SMF status was independently associated with the risk of thrombosis independently of higher WBC, presence of chronic kidney disease [9] and higher estimated plasma volume status (calculated based on hemoglobin and hematocrit values using the Strauss derived Duarte formula) [10, 11] while controlling for other factors known to be associated with higher thrombotic risk. These important findings need to be validated in independent cohorts of patients and if confirmed, may improve individual risk assessment in patients with myelofibrosis.

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Table 1: Patients' characteristics in an overall cohort stratified according to the etiology of myelofibrosis.

	PMF (177 pts)	Post-ET SMF (34 pts)	Post-PV SMF (37 pts)	P value
Age (years)	68 IQR (60 - 75)	67 IQR (60 - 73.75)	68 IQR (61 - 76)	0.798
Sex				
Male	115/177 (65%)	22/34 (64.7%)	15/37 (40.5%)	0.019 *
Female	62/177 (35%)	12/34 (35.3%)	22/37 (59.5%)	
BM fibrosis				
Grade 0-I	76/177 (42.9%)	0/34 (0%)	0/37 (0%)	0.001 *
Grade II-III	101/177 (57.1%)	34/34 (100%)	37/37 (100%)	
JAK2 mutated	114/169 (67.5%)	22/32 (68.8%)	34/35 (97.1%)	0.002 *
CALR mutated	17/138 (12.3%)	4/25 (16%)	0/35 (0%)	0.069
MPL mutated	4/136 (2.9%)	0/24 (0%)	0/35 (0%)	0.412
Constitutional symptoms	70/177 (39.5%)	12/34 (35.3%)	23/37 (62.2%)	0.027 *
Transfusion dependency	46/177 (26%)	8/34 (23.5%)	6/37 (16.2%)	0.449
Massive splenomegaly	38/144 (26.4%)	1/20 (5%)	12/27 (44.4%)	0.010 *
Spleen size under left costal margin (cm)	3 IQR (0 - 8)	1 IQR (0 - 5)	7 IQR (4 - 11)	<0.001 *

	PMF (177 pts)	Post-ET SMF (34 pts)	Post-PV SMF (37 pts)	P value
Blast phase disease	5/177 (2.8%)	1/34 (2.9%)	4/37 (10.8%)	0.076
WBC (x10⁹/L)	10.7 IQR (6.78 - 18)	8.5 IQR (5.63 - 14.5)	14.7 IQR (9.6 - 20.8)	0.033 *
Circulatory blasts ≥1%	56/177 (31.6%)	17/34 (50%)	19/37 (51.4%)	0.019 *
Abs. mono. (x10⁹/L)	0.5 IQR (0.3 - 0.93)	0.5 IQR (0.3 - 0.7)	0.4 IQR (0.21 - 0.61)	0.218
Abs. basophils (x10⁹/L)	0.1 IQR (0.07 - 0.3)	0.1 IQR (0.02 - 0.2)	0.2 IQR (0.09 - 0.4)	0.068
Abs. lymphocytes (x10⁹/L)	1.6 IQR (1.2 - 2.3)	1.5 IQR (1.2 - 2.12)	1.2 IQR (0.95 - 1.6)	0.042 *
Hemoglobin level (g/L)	115 IQR (92 - 134)	106.5 IQR (94.5 - 119.75)	120 IQR (100 - 144)	0.136
Hematocrit ≥45%	26/168 (15.5%)	2/34 (5.9%)	10/36 (27.8%)	0.042 *
MCV (fL)	86.9 IQR (82.5 - 92.4)	90.2 IQR (85.23 - 98.4)	89 IQR (84.1 - 101.6)	0.013 *
MCHC (g/L)	322 IQR (309 - 330)	317 IQR (310.5 - 330)	313.5 IQR (303.5 - 325.25)	0.077
RDW (%)	19.1 IQR (17.15 - 21.45)	19.2 IQR (17.53 - 21.05)	20 IQR (18.7 - 20.9)	0.329
ePVS (dl/g)	5.6 IQR (4.41 - 7.89)	6.3 IQR (5.36 - 7.4)	5.1 IQR (3.97 - 6.98)	0.121
Platelets (x10⁹/L)	366 IQR (199 - 612)	440.5 IQR (229.75 - 666.75)	291 IQR (207 - 403)	0.086
MPV (fL)	9.5 IQR (8.5 - 10.5)	9.3 IQR (8.6 - 10.25)	9.8 IQR (8.55 - 10.6)	0.654
LDH (U/L)	453 IQR (300.75 - 692.25)	415.5 IQR (308.75 - 612.5)	472 IQR (339 - 715)	0.702
CRP (mg/L)	4.5 IQR (1.18 - 13.03)	3.8 IQR (1.6 - 7.2)	6.3 IQR (2.6 - 11.4)	0.241

	PMF (177 pts)	Post-ET SMF (34 pts)	Post-PV SMF (37 pts)	P value
Albumin (g/L)	43 IQR (40 - 47)	43.5 IQR (41 - 45.53)	41 IQR (38 - 43)	0.014 *
Uric acid (mmol/L)	406 IQR (326.5 - 473)	361 IQR (272 - 420)	344 IQR (302.25 - 409.75)	0.009 *
Fe (μmol/L)	14.1 IQR (8.5 - 18.1)	14.4 IQR (9.9 - 18.2)	7.5 IQR (4 - 12.98)	0.011 *
TIBC (μmol/L)	51.4 IQR (46.5 - 57.7)	49.1 IQR (44.55 - 60.63)	55 IQR (39 - 62.7)	0.874
Transferrin saturation (%)	27.4 IQR (14.95 - 37.05)	27.9 IQR (21.75 - 33.79)	12.4 IQR (7.27 - 31.6)	0.077
Ferritin (μg/L)	201 IQR (65.5 - 405)	128 IQR (59.75 - 182.25)	130.5 IQR (29.7 - 253.5)	0.348
Charlson comorbidity index	3 IQR (2 - 4.25)	3 IQR (2 - 4)	2 IQR (2 - 4)	0.513
CV risk factors	120/158 (75.9%)	24/32 (75%)	17/32 (53.1%)	0.029 *
Chronic kidney disease	27/128 (21.1%)	1/19 (5.3%)	3/29 (10.3%)	0.127
Arterial hypertension	97/158 (61.4%)	20/33 (60.6%)	15/35 (42.9%)	0.127
Diabetes mellitus	28/160 (17.5%)	2/33 (6.1%)	5/35 (14.3%)	0.248
Hyperlipoproteinemia	24/150 (16%)	6/31 (19.4%)	5/34 (14.7%)	0.867
Obesity	8/122 (6.6%)	0/19 (0%)	0/26 (0%)	0.212
History of thrombosis	22/177 (12.4%)	10/34 (29.4%)	7/37 (18.9%)	0.038 *

	PMF (177 pts)	Post-ET SMF (34 pts)	Post-PV SMF (37 pts)	P value
DIPSS (PMF)				
Low risk	27/177 (15.3%)	-		
Intermediate-1 risk	67/177 (37.9%)			
Intermediate-2 risk	69/177 (39%)			
High risk	14/177 (7.9%)		-	-
MYSEC-PM (SMF)				
Low risk		4/25 (16%)	4/35 (11.4%)	
Intermediate-1 risk		10/25 (40%)	12/35 (34.3%)	
Intermediate-2 risk		6/25 (24%)	9/35 (25.7%)	
High risk	-	5/25 (20%)	10/35 (28.6%)	0.848

*statistically significant at level $P < 0.05$ / Abbreviations: pts – patients, PMF – primary myelofibrosis, PV – polycythemia vera, SMF – secondary myelofibrosis, ET – essential thrombocythemia, BM – bone marrow, JAK2 – Janus kinase 2, CALR – Calreticulin, MPL – thrombopoietin receptor, Massive splenomegaly – palpable spleen ≥ 10 cm under the left costal margin, WBC – white blood cells, Abs. – absolute, MCV – mean corpuscular volume, MCHC – mean corpuscular hemoglobin concentration, RDW – red blood cell distribution width, ePVS=estimated plasma volume calculated according to the Strauss method, MPV – mean platelet volume, LDH – lactate dehydrogenase, CRP – C reactive protein, Fe – serum

iron, TIBC – total iron binding capacity, CV – cardiovascular, MDRD eGFR – Modification of Diet in Renal Disease estimated glomerular filtration rate, DIPSS – Dynamic International Prognostic Scoring System, MYSEC-PM – myelofibrosis secondary to PV and ET prognostic model.

Figure 1: A) Overall survival, **B)** Time to arterial thrombosis and **C)** time to bleeding stratified according to the etiology of myelofibrosis.

