

Supplemental Index: Persistent leukocytosis in polycythemia vera is associated with disease evolution but not thrombosis: an analysis from a 520-patient retrospective multi-center database

Supplemental Table S1: Summary of goodness-of-fit statistics for 12-month HCT, WBC, and PLT trajectory groups.

Optimal number of groups for 12 Month HCT; N=440						Optimal number of groups for 12 Month WBC; N=440						Optimal number of groups for 12 Month Platelet Counts; N=440					
HCT	Number of Groups				Selected Model	WBC	Number of Groups				Selected Model	Platelet	Number of Groups				Selected Model
	1	2	3	4			1	2	3	4			1	2	3	4	
Log likelihood	-5914.9	-5767.2	-5660.8	-5625.6	-5647.3	Log likelihood	-1449.8	-1130.2	-978.4	-879.5	-872.6	Log likelihood	-1759.8	-1412.3	-1271.4	-1185.2	-1271.5
BIC	-5927.1	-5791.6	-5697.3	-5674.2	-5686.9	BIC	-1461.9	-1154.6	-1014.9	-928.2	-924.3	BIC	-1771.9	-1436.7	-1307.9	-1233.9	-1305.0
Entropy	-	116.35	93.72	110.79	91.00	Entropy	-	47.76	89.61	87.58	85.43	Entropy	-	52.37	68.74	100.98	68.95
Entropy (relative)	-	0.62	0.81	0.82	0.81	Entropy (relative)	-	0.84	0.81	0.86	0.86	Entropy (relative)	-	0.83	0.86	0.83	0.86
Two-group model	1	2	3	4		Two-group model	1	2	3	4		Two-group model	1	2	3	4	
1. n, 258 (59%)	0.854	0.146				1. n, 318 (72%)	0.963	0.037				1. n, 162 (37%)	0.923	0.077			
2. n, 182 (41%)	0.099	0.901				2. n, 122 (28%)	0.058	0.942				2. n, 278 (63%)	0.038	0.962			
Three-group model	1	2	3			Three-group model	1	2	3			Three-group model	1	2	3		
1. n, 36 (8%)	0.881	0.119	0			1. n, 130 (30%)	0.91	0.09	0			1. n, 36 (8%)	0.918	0.082	0		
2. n, 293 (67%)	0.011	0.931	0.058			2. n, 240 (54%)	0.057	0.910	0.033			2. n, 183 (42%)	0.011	0.931	0.058		
3. n, 111 (25%)	0	0.123	0.877			3. n, 70 (16%)	0	0.077	0.923			3. n, 221 (50%)	0	0.060	0.940		
Four-group model	1	2	3	4		Four-group model	1	2	3	4		Four-group model	1	2	3	4	
1. n, 35 (8%)	0.887	0.021	0.092	0		1. n, 105 (24%)	0.91	0.09	0	0		1. n, 17 (4%)	0.948	0.052	0	0	
2. n, 20 (4%)	0.005	0.857	0.118	0.02		2. n, 222 (50%)	0.048	0.923	0.029	0		2. n, 118 (27%)	0.007	0.929	0.064	0	
3. n, 272 (62%)	0.011	0.028	0.91	0.051		3. n, 97 (22%)	0	0.067	0.926	0.006		3. n, 205 (47%)	0	0.051	0.889	0.059	
4. n, 113 (26%)	0	0.02	0.088	0.892		4. n, 16 (4%)	0	0	0.06	0.94		4. n, 100 (23%)	0	0	0.094	0.906	
Selected Model						Selected Model						Selected Model					
1. n, 36 (8%)	0.893	0.107	0			1. n, 106 (24%)	0.912	0.088	0	0		1. n, 36 (8%)	0.92	0.08	0		
2. n, 295 (67%)	0.012	0.929	0.059			2. n, 222 (50%)	0.047	0.926	0.027	0.000		2. n, 183 (42%)	0.011	0.932	0.057		
3. n, 109 (25%)	0	0.115	0.885			3. n, 97 (22%)	0	0.066	0.925	0.009		3. n, 221 (50%)	0	0.062	0.938		
						4. n, 15 (3%)	0	0	0.044	0.956							
Intercepts (I) and Linear, Quadratic and Cubic Slopes for Final Selected Model: G1: I = 32.74 (0.89), L = 0.24 (0.11); G2: I = 45.55 (0.42), L = -1.38 (0.29), Q = 0.17 (0.06), C = -0.006 (0.003); G3: I = 57.40 (0.73), L = -4.97 (0.50), Q = 0.62 (0.10), C = -0.02 (0.005)						Intercepts (I) and Linear, Quadratic and Cubic Slopes for Final Selected Model: G1: I = 1.96 (0.04), L = -0.17 (0.03), Q=0.02 (0.006), C=-0.0009 (0.0004); G2: I = 2.34 (0.03), L = -0.09 (0.02), Q = 0.012 (0.004), C = -0.0005 (0.0002); G3: I = 2.74 (0.02); G4: I=3.44 (0.09), L=0.17 (0.08), Q=-0.03 (0.02), C=0.002 (0.0009)						Intercepts (I) and Linear, Quadratic and Cubic Slopes for Final Selected Model: G1: I = 4.87 (0.08), L = -0.06 (0.03), Q=0.004 (0.002); G2: I = 5.79 (0.04), L = -0.06 (0.012), Q = 0.003 (0.001); G3: I = 6.41 (0.03), L=-0.01 (0.003)					
Shaded cells are statistics for the selected model																	
Bold values represent the mean posterior probability values for each group within each model																	

Supplemental Table S2: Comparison of baseline characteristics of thrombosis and evolution cohorts included in multivariable Cox proportional hazards models to those excluded for loss to follow up or event within trajectory modeling period.

Thrombosis		
Characteristic	Included in Trajectory Modeling	Included in Cox Modeling
Patients (N)	440	377
Age at diagnosis, years		
Median (Min-Max)	58 (20-93)	58 (20-93)
Male, N (%)	213 (48%)	181 (48%)
Duration of disease prior to contact, months		
Median (Min-Max)	2 (0-358)	2 (0-358)
Prior Thrombosis N(%)	110 (25%)	93 (25%)
Number of cardiovascular risk factors (median)		
Diabetes, N (%)	45 (10%)	38 (10%)
Hypertension, N (%)	180 (41%)	151 (40%)
Hyperlipidemia, N (%)	107 (24%)	90 (24%)
Coronary Artery Disease, N (%)	41 (9%)	36 (10%)
History of Smoking, N (%)	110 (25%)	97 (26%)
Evolution		
Characteristic	Included in Trajectory Modeling	Included in Cox Modeling
Patients (N, %)	440	378
Age at diagnosis, years		
Median (Min-Max)	58 (20 – 93)	58 (20-93)
Duration of disease (prior to contact), months		
Median (Min-Max)	2 (0 – 358)	2 (0-358)

Supplemental Table S3: Summary and distribution of baseline characteristics of patient cohorts across 12-month WBC, HCT, and PLT trajectory groups.

WBC and thrombosis

Characteristic	Overall	WBC5	WBC10	WBC15	WBC35	p
Patients N (%)	377	93 (25%)	189 (50%)	81 (21%)	14 (4%)	
Age at diagnosis, years						0.9118
Median (range)	58 (20-93)	59 (22-90)	57 (20-93)	58 (22-91)	57 (36-75)	
Gender						0.6132
Male N (%)	181 (48%)	42 (45%)	89 (47%)	44 (54%)	6 (43%)	
Duration of disease (prior to contact), months						0.0143
Median (range)	2 (0-358)	1 (0-312)	2 (0-358)	11 (0-356)	30 (0-165)	
Prior Thrombosis N (%)	93 (25%)	32 (34%)	48 (25%)	11 (14%)	2 (14%)	0.0119
Number of cardiovascular risk factors (median)	1	1	1	1	1	
Diabetes N (%)	38 (10%)	7 (8%)	18 (10%)	11 (14%)	2 (14%)	0.5516
Hypertension N (%)	151 (40%)	35 (38%)	76 (40%)	35 (43%)	5 (36%)	0.8792
Hyperlipidemia N (%)	90 (24%)	20 (22%)	44 (23%)	20 (25%)	6 (43%)	0.3721
Coronary Artery Disease (N, %)	36 (10%)	9 (10%)	21 (11%)	5 (6%)	1 (7%)	0.6373
History of Smoking N (%)	97 (26%)	24 (26%)	44 (23%)	27 (33%)	2 (14%)	0.2611
Pack-years, median (range)	12 (0.3-90)	20 (0.3 – 60)	15 (1-81)	8.25 (0.5-90)	3 (1-5)	0.3827
Period of phlebotomy-only during trajectory period N(%)	118 (31%)	15 (16%)	69 (37%)	29 (36%)	5 (35%)	0.0042
On aspirin during trajectory period N(%)	340 (90%)	85 (91%)	165 (87%)	76 (94%)	14 (100%)	0.1978
On hydroxyurea during trajectory period N(%)	226 (60%)	61 (66%)	117 (62%)	41 (51%)	7 (50%)	0.1682
On Ruxolitinib during trajectory period N(%)	40 (11%)	5 (5%)	20 (11%)	13 (16%)	2 (14%)	0.1440
On pegIFN-a2a during trajectory period N(%)	34 (9%)	11 (12%)	19 (10%)	4 (5%)	0 (0%)	0.2435

WBC and evolution

Characteristic	Overall	WBC5	WBC10	WBC15	WBC35	p
Patients (N, %)	378	94	193	80	11	
Age at diagnosis, years						0.9824
Median (range)	58 (20-93)	59 (22-90)	58 (20-93)	59 (22-91)	55 (36-76)	
Duration of disease (prior to contact), months						0.0849
Median (range)	2 (0-358)	2 (0-312)	1 (0-358)	9 (9-356)	41(0-151)	
Period of phlebotomy-only during trajectory period N(%)	120 (32%)	16 (17%)	71 (37%)	29 (36%)	4 (36%)	0.0058
On aspirin during trajectory period N(%)	341 (90%)	85 (90%)	170 (88%)	75 (94%)	11 (100%)	0.3444
On hydroxyurea during trajectory period N(%)	223 (59%)	61 (65%)	119 (62%)	39 (49%)	4 (36%)	0.0522
On Ruxolitinib during trajectory period N(%)	38 (10%)	5 (5%)	20 (10%)	12 (15%)	1 (9%)	0.2099
On pegIFN-a2a during trajectory period N(%)	34 (9%)	11 (12%)	19 (10%)	4 (5%)	0 (0%)	0.3007

Hematocrit and thrombosis

Characteristic	Overall	HCT35	HCT43	HCT47	p
Patients N (%)	377	28 (7%)	256 (68%)	93 (25%)	

Age at diagnosis, years					<i>0.0304</i>
Median (range)	58 (20-93)	56 (24-82)	57 (20-93)	62 (21-91)	
Gender					<i><0.0001</i>
Male N (%)	181 (48%)	4 (14%)	110 (43%)	67 (72%)	
Duration of disease (prior to contact), months					<i><0.0001</i>
Median (range)	2 (0-358)	48 (0-237)	6 (0-358)	0 (0-163)	
Prior Thrombosis N (%)	93 (25%)	11 (39%)	66 (26%)	16 (17%)	<i>0.0455</i>
Number of cardiovascular risk factors (median)	1	0	1	1	
Diabetes N (%)	38 (10%)	2 (7%)	26 (10%)	10 (11%)	<i>0.8545</i>
Hypertension N (%)	151 (40%)	10 (36%)	95 (37%)	46 (50%)	<i>0.1016</i>
Hyperlipidemia N (%)	90 (24%)	4 (14%)	63 (25%)	23 (25%)	<i>0.4653</i>
Coronary Artery Disease N (%)	36 (10%)	3 (11%)	24 (9%)	9 (10%)	<i>0.9730</i>
History of Smoking N (%)	97 (26%)	5 (18%)	65 (25%)	27 (29%)	<i>0.4833</i>
Pack-years, median (range)	12 (0.3-90)	13.75 (0-30)	12 (0-81)	12.5 (0-90)	<i>0.7959</i>
Period of phlebotomy-only during trajectory period N(%)	118 (31%)	4 (14%)	77 (30%)	37 (40%)	<i>0.0293</i>
On aspirin during trajectory period N(%)	340 (90%)	26 (93%)	232 (91%)	82 (88%)	<i>0.7020</i>
On hydroxyurea during trajectory period N(%)	226 (60%)	17 (61%)	148 (58%)	61 (66%)	<i>0.4218</i>
On Ruxolitinib during trajectory period N(%)	40 (11%)	4 (14%)	25 (10%)	11 (12%)	<i>0.6918</i>
On pegIFN-a2a during trajectory period N(%)	34 (9%)	2 (7%)	24 (9%)	8 (9%)	<i>0.9142</i>
Hematocrit and evolution					
Characteristic	Overall	HCT35	HCT43	HCT45	p
Patients N (%)	378	21 (5%)	261 (69%)	96 (25%)	
Age at diagnosis, years					<i>0.0387</i>
Median (range)	58 (20-93)	57 (24-82)	58 (20-93)	62 (21-91)	
Duration of disease (prior to contact), months					<i><0.0001</i>
Median (range)	2 (0-358)	13 (0-167)	6 (0-358)	0 (0-163)	
Period of phlebotomy-only during trajectory period N(%)	120 (32%)	3 (14%)	78 (30%)	39 (41%)	<i>0.0323</i>
On aspirin during trajectory period N(%)	341 (90%)	20 (95%)	237 (91%)	84 (88%)	<i>0.4714</i>
On hydroxyurea during trajectory period N(%)	223 (59%)	11 (52%)	150 (57%)	62 (65%)	<i>0.3927</i>
On Ruxolitinib during trajectory period N(%)	38 (10%)	3 (14%)	25 (10%)	10 (10%)	<i>0.7807</i>
On pegIFN-a2a during trajectory period N(%)	34 (9%)	2 (10%)	24 (9%)	8 (8%)	<i>0.9650</i>
Platelet and thrombosis					
Characteristic	Overall	PLT125	PLT300	PLT600	p
Patients N (%)	377	33 (9%)	158 (42%)	186 (49%)	
Age at diagnosis, years					<i>0.0004</i>
Median (range)	58 (20-93)	57 (36-87)	63 (21-93)	54 (20-91)	
Gender					<i>0.0292</i>
Male N (%)	181 (48%)	20 (61%)	84 (53%)	77 (41%)	
Duration of disease (prior to contact), months					<i>0.3204</i>
Median (range)	2 (0-358)	16 (0-232)	1 (0-356)	3 (0-358)	
Prior Thrombosis N (%)	93 (25%)	8 (24%)	45 (28%)	40 (22%)	<i>0.3262</i>
Number of cardiovascular risk factors (median)	1	1	1	1	
Diabetes N (%)	38 (10%)	3 (9%)	15 (9%)	20 (11%)	<i>0.9101</i>
Hypertension N (%)	151 (40%)	15 (45%)	67 (42%)	69 (37%)	<i>0.4863</i>
Hyperlipidemia N (%)	90 (24%)	9 (27%)	43 (27%)	38 (20%)	<i>0.3021</i>

Coronary Artery Disease N (%)	36 (10%)	3 (9%)	20 (13%)	13 (7%)	0.2032
History of Smoking N (%)	97 (26%)	10 (30%)	50 (32%)	37 (20%)	0.0374
Pack-years, median (range)	12.5	12 (1-40)	13.75 (0.3-90)	12 (0.5-45)	0.2269
Period of phlebotomy-only during trajectory period N(%)	118 (31%)	10 (30%)	44 (28%)	64 (34%)	0.4218
On aspirin during trajectory period N(%)	340 (90%)	30 (91%)	140 (89%)	170 (91%)	0.6795
On hydroxyurea during trajectory period N(%)	226 (60%)	21 (64%)	102 (65%)	103 (55%)	0.2015
On Ruxolitinib during trajectory period N(%)	40 (11%)	4 (12%)	13 (8%)	23 (12%)	0.4428
On pegIFN-a2a during trajectory period N(%)	34 (9%)	4 (12%)	11 (7%)	19 (10%)	0.4662
Platelet and evolution					
Characteristic	Overall	PLT125	PLT300	PLT600	p
Patients N (%)	378	26 (7%)	157 (41%)	195 (52%)	
Age at diagnosis, years					0.0009
Median (range)	58 (20-93)	58 (36-87)	63 (21-93)	55 (20-91)	
Duration of disease (prior to contact), months					0.2854
Median (range)	2 (0-358)	4 (0-177)	1 (0-356)	4 (0-358)	
Period of phlebotomy-only during trajectory period N(%)	120 (32%)	8 (31%)	45 (29%)	67 (34%)	0.5182
On aspirin during trajectory period N(%)	341 (90%)	25 (96%)	138 (88%)	178 (91%)	0.3256
On hydroxyurea during trajectory period N(%)	223 (59%)	19 (73%)	102 (65%)	102 (52%)	0.0178
On Ruxolitinib during trajectory period N(%)	38 (10%)	3 (12%)	13 (8%)	22 (11%)	0.6266
On pegIFN-a2a during trajectory period N(%)	34 (9%)	4 (15%)	11 (7%)	19 (10%)	0.3347

Supplemental Table S4: Survival analysis examining association between CBC trajectories and hazard of thrombosis with exclusion of patients experiencing superficial thrombotic events.

Thrombosis					
	Event Rate	Median time-to-event (months)	HR ¹ [95% CI]	p	Overall p
Leukocyte trajectory					
WBC5	4/92 (4%)	24.4	Reference		0.3128
WBC10	21/189 (11%)	35.0	2.75 [0.92-8.18]	0.0696	
WBC15	5/79 (6%)	32.0	1.86 [0.48-7.15]	0.3694	
WBC35	1/14 (7%)	24.1	2.91 [0.30-27.96]	0.3544	
Overall	31/374 (9%)				
HCT Trajectory					
HCT35	3/28 (11%)	34.8	0.99 [0.23-4.31]	0.9937	0.1820
HCT43	16/254 (6%)	29.8	0.50 [0.22-1.14]	0.1009	
HCT47	12/92 (13%)	29.1	Reference		
Overall	31/374 (9%)				
PLT Trajectory					
PLT125	3/32 (9%)	26.6	Reference		0.8444
PLT300	13/157 (8%)	32.0	0.71 [0.20-2.55]	0.6034	
PLT600	15/185 (8%)	31.7	0.85 [0.24-3.00]	0.7961	
Overall	31/374 (9%)				

¹ Multivariable HR adjusted for age at diagnosis, sex, duration of disease at time of institutional contact, sum of cardiovascular risk factors (diabetes, hypertension, hyperlipidemia, coronary artery disease, smoking), and whether or not the patient was on cytoreductive therapy (hydroxyurea, PEGinterferon-alfa, or Ruxolitinib) at some point during landmark trajectory modeling period.