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ORIGINAL ARTICLE

Analysis of Blood Group Antigens as Risk Factors for Thrombosis in Polycythemia Vera Patients

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SUMMARY

Background: **Polycythemia vera (PV) is characterized by the abnormal proliferation of red blood cells (RBCs). Thrombosis and associated cardiovascular diseases are leading causes of mortality in patients with PV. This study aimed to investigate the association of Lutheran/BCAM (CD239) and other RBC antigens with thrombosis in PV.**
Materials and Methods: **This single-center, prospective study consecutively enrolled 50 PV patients, 39 with secondary polycythemia, and 20 healthy controls (HC) who visited the apheresis unit for phlebotomy between May 2022 and September 2023. The normalized expression levels of Lutheran/BCAM (CD239), Indian (CD44), LW/ICAM (CD242), and Rh-related integrin-associated protein (IAP, CD47) antigens were assessed by flow cytometry. *JAK2*V617F expression was quantified and coagulation parameters were analyzed. Laboratory and clinical data were retrieved from the medical records.**
Results: **PV patients exhibited significantly higher mean fluorescence intensity (MFI) for Lutheran/BCAM: 45.2 ± 32.8 vs. 33.0 ± 14.4, p = 0.047, Indian (CD44): 13.5 ± 18.4 vs. 8.6 ± 1.1, p = 0.195, and IAP (CD47): 604.8 ± 193.2 vs. 514.9 ± 63.2, p = 0.036 compared to HC. The Indian (CD44) antigen was identified as a risk factor for thrombosis with an odds ratio (OR) of 1.359 (95% confidence interval [CI]: 1.003 - 1.842) in a multivariable model. Positive *JAK2* measurable residual disease (*JAK2*-MRD) (expression was detected in 100% (25/25) of PV patients assessed, with a median variant allele frequency of 51.8% (95% CI: 45.4 - 65.0%).**
Conclusions: **Higher expression of Indian (CD44) MFI levels in RBCs were associated with thrombotic events in patients with PV. Assessing RBC Indian (CD44) expression may serve as a potential biomarker for thrombotic risk stratification and prevention in PV.**
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Supplementary Data

Table S1. Thrombotic events in polycytemia vera and secondary polycythemia study patients.

	n	%	n	%
	PV (8/50)	16.0	Secondary polycythemia (2/37)	5.4
Arterial thrombosis	7/8	87.5	2/2	100
Transient ischemic attack	0	0	0	0
Stroke	0	0	0	0
Myocardial infarction	7	87.5	2	100
Venous thrombosis	1/8	12.5	0/2	0
Deep vein thrombosis	0	0	0	0
Splanchnic vein thrombosis	1	12.5	0	0

PV polycythemia vera.

Table S2. Tukey's multiple post hoc comparisons of laboratory characteristics.

Laboratory characteristics	(I) group	(J) group	Mean difference (I - J)	Std. Error	p-value
WBC	1	2	3,262.90	764.42	< 0.001 *
		3	4,370.90	917.68	< 0.001 *
	2	1	-3,262.97	764.42	< 0.001 *
		3	1,107.93	972.25	0.492
Hb	1	2	-1.36	0.36	0.001 *
		3	1.30	0.44	0.010 *
	2	1	1.36	0.36	0.001 *
		3	2.66	0.46	< 0.001 *
Platelet	1	2	186.60	29.02	< 0.001 *
		3	159.74	34.84	< 0.001 *
	2	1	-186.60	29.02	< 0.001 *
		3	-26.86	36.91	0.748
PT	1	2	0.06	0.02	0.001 *
		3	0.07	0.02	0.002 *
	2	1	-0.06	0.02	0.001 *
		3	0.01	0.02	0.938
Lutheran/BCAM (CD239)	1	2	1.00	6.04	0.985
		3	17.01 *	7.08	0.047 *
	2	1	-1.00	6.04	0.985
		3	16.02	7.44	0.085
LW/ICAM (CD242)	1	2	0.28	0.37	0.741
		3	-0.02	0.44	0.998
	2	1	-0.28	0.37	0.741
		3	-0.30	0.45	0.788
Indian (CD44)	1	2	10.28	6.16	0.223
		3	12.77	7.33	0.195
	2	1	-10.28	6.16	0.223

Table S2. Tukey's multiple post hoc comparisons of laboratory characteristics (continued).

Laboratory characteristics	(I) group	(J) group	Mean difference (I - J)	Std. Error	p-value
Indian (CD44)		3	2.49	7.78	0.945
Rh-related IAP (CD47)	1	2	-10.98	36.95	0.953
		3	110.54 *	43.92	0.036 *
	2	1	10.98	36.95	0.953
		3	121.52 *	46.65	0.028 *
aPTT	1	2	2.04	0.52	< 0.001 *
		3	0.49	0.62	0.708
	2	1	-2.04	0.52	< 0.001 *
		3	-1.55	0.66	0.054
Fibrinogen	1	2	9.08	15.99	0.838
		3	-5.07	19.03	0.962
	2	1	-9.08	15.99	0.838
		3	-14.15	20.27	0.765
Antithrombin III	1	2	4.16	2.85	0.313
		3	-1.12	3.39	0.942
	2	1	-4.16	2.85	0.313
		3	-5.28	3.61	0.313
FDP	1	2	-3.89	2.81	0.352
		3	0.18	3.31	0.998
	2	1	3.89	2.81	0.352
		3	4.06	3.55	0.488
Factor VIII	1	2	-6.80	9.66	0.762
		3	-16.69	11.59	0.325
	2	1	6.80	9.66	0.762
		3	-9.89	12.28	0.701
Protein S	1	2	-24.80	6.64	0.001 *
		3	-21.44	8.12	0.026 *
	2	1	24.80	6.64	0.001 *
		3	3.36	8.58	0.919
Protein C	1	2	-3.37	4.88	0.769
		3	-7.89	5.85	0.372
	2	1	3.37	4.88	0.769
		3	-4.52	6.20	0.747
Lupus anticoagulant	1	2	-0.07	0.03	0.027 *
		3	-0.10	0.03	0.017 *
	2	1	0.07	0.03	0.027 *
		3	-0.02	0.04	0.832

*** Group 1 represents polycythemia vera patients, group 2 for secondary polycythemia patients and group 3 for healthy controls.**

Table S3. Mutations identified in *CD44* gene, chromosome position, mutation type, nucleotide change, amino acid change.

Patient no.	Chromosome position	Mutation type	Nucleotide change	Amino acid change
1	Chr. 11: 35,176,485	intron	c.68-90A>G	.
	Chr. 11: 35,200,315	intron	c.923-767T>A *	.
	Chr. 11: 35,201,611	intron	c.1037-60T>C *	.
	Chr. 11: 35,204,608	missense	c.1250A>G *	p.Lys417Arg
	Chr. 11: 35,208,126	missense	c.1436T>C *	p.Ile479Thr
	Chr. 11: 35,219,242	intron	c.1874-74T>A	.
	Chr. 11: 35,222,497	3_prime_UTR	c.*119G>C *	.
	Chr. 11: 35,222,511	3_prime_UTR	c.*133A>G *	.
2	Chr. 11: 35,150,575	intron	c.67+11205G>A	.
	Chr. 11: 35,153,498	intron	c.67+14128T>C	.
	Chr. 11: 35,176,485	intron	c.68-90A>G	.
	Chr. 11: 35,200,315	intron	c.923-767T>A *	.
	Chr. 11: 35,201,611	intron	c.1037-60T>C *	.
	Chr. 11: 35,204,608	missense	c.1250A>G *	p.Lys417Arg
	Chr. 11: 35,208,126	missense	c.1436T>C *	p.Ile479Thr
	Chr. 11: 35,222,497	3_prime_UTR	c.*119G>C *	.
	Chr. 11: 35,222,511	3_prime_UTR	c.*133A>G *	.
3	Chr. 11: 35,176,485	intron	c.68-90A>G	.
	Chr. 11: 35,200,315	intron	c.923-767T>A *	.
	Chr. 11: 35,201,611	intron	c.1037-60T>C *	.
	Chr. 11: 35,204,608	missense	c.1250A>G *	p.Lys417Arg
	Chr. 11: 35,208,126	missense	c.1436T>C *	p.Ile479Thr
	Chr. 11: 35,219,242	intron	c.1874-74T>A	.
	Chr. 11: 35,222,497	3_prime_UTR	c.*119G>C *	.
	Chr. 11: 35,222,511	3_prime_UTR	c.*133A>G *	.
4	Chr. 11: 35,176,485	intron	c.68-90A>G	.
	Chr. 11: 35,200,315	intron	c.923-767T>A *	.
	Chr. 11: 35,200,358	intron	c.923-724G>A	.
	Chr. 11: 35,201,611	intron	c.1037-60T>C *	.
	Chr. 11: 35,204,608	missense	c.1250A>G *	p.Lys417Arg
	Chr. 11: 35,208,126	missense	c.1436T>C *	p.Ile479Thr
	Chr. 11: 35,219,242	intron	c.1874-74T>A	.
	Chr. 11: 35,222,497	3_prime_UTR	c.*119G>C *	.
	Chr. 11: 35,222,511	3_prime_UTR	c.*133A>G *	.
5	Chr. 11: 35,150,575	intron	c.67+11205G>A	.
	Chr. 11: 35,153,498	intron	c.67+14128T>C	.
	Chr. 11: 35,169,898	intron	c.68-6677C>G	.
	Chr. 11: 35,170,667	intron	c.68-5908G>A	.
	Chr. 11: 35,170,732	intron	c.68-5843A>G	.
	Chr. 11: 35,171,082	intron	c.68-5493C>T	.
	Chr. 11: 35,176,485	intron	c.68-90A>G	.
	Chr. 11: 35,176,561	intron	c.68-14A>G	.
	Chr. 11: 35,180,435	intron	c.367+28C>T	.
	Chr. 11: 35,200,315	intron	c.923-767T>A *	.

Table S3. Mutations identified in *CD44* gene, chromosome position, mutation type, nucleotide change, amino acid change (continued).

Patient no.	Chromosome position	Mutation type	Nucleotide change	Amino acid change
5	Chr. 11: 35,201,611	intron	c.1037-60T>C *	.
	Chr. 11: 35,204,608	missense	c.1250A>G *	p.Lys417Arg
	Chr. 11: 35,208,126	missense	c.1436T>C *	p.Ile479Thr
	Chr. 11: 35,219,242	intron	c.1874-74T>A	.
	Chr. 11: 35,222,497	3_prime_UTR	c.*119G>C *	.
	Chr. 11: 35,222,511	3_prime_UTR	c.*133A>G *	.
6	Chr. 11: 35,171,009	intron	c.68-5566C>T	.
	Chr. 11: 35,176,485	intron	c.68-90A>G	.
	Chr. 11: 35,200,315	intron	c.923-767T>A *	.
	Chr. 11: 35,201,611	intron	c.1037-60T>C *	.
	Chr. 11: 35,204,608	missense	c.1250A>G *	p.Lys417Arg
	Chr. 11: 35,208,126	missense	c.1436T>C *	p.Ile479Thr
	Chr. 11: 35,222,497	3_prime_UTR	c.*119G>C *	.
	Chr. 11: 35,222,511	3_prime_UTR	c.*133A>G *	.
10	Chr. 11: 35,153,406	intron	c.67+14043dupT	.
	Chr. 11: 35,158,104	intron	c.68-18471G>A	.
	Chr. 11: 35,162,980	intron	c.68-13595C>T	.
	Chr. 11: 35,163,005	intron	c.68-13570A>T	.
	Chr. 11: 35,166,644	intron	c.68-9931G>A	.
	Chr. 11: 35,166,742	intron	c.68-9833C>T	.
	Chr. 11: 35,169,898	intron	c.68-6677C>G	.
	Chr. 11: 35,170,567	intron	c.68-6008G>A	.
	Chr. 11: 35,171,082	intron	c.68-5493C>T	.
	Chr. 11: 35,176,485	intron	c.68-90A>G	.
	Chr. 11: 35,176,561	intron	c.68-14A>G	.
	Chr. 11: 35,200,315	intron	c.923-767T>A *	.
	Chr. 11: 35,200,363	intron	c.923-719T>C	.
	Chr. 11: 35,201,611	intron	c.1037-60T>C *	.
	Chr. 11: 35,201,769	missense	c.1135C>G	p.Pro379Ala
	Chr. 11: 35,204,608	missense	c.1250A>G *	p.Lys417Arg
	Chr. 11: 35,208,126	missense	c.1436T>C *	p.Ile479Thr
	Chr. 11: 35,219,242	intron	c.1874-74T>A	.
	Chr. 11: 35,222,497	3_prime_UTR	c.*119G>C *	.
	Chr. 11: 35,222,511	3_prime_UTR	c.*133A>G *	.
11	Chr. 11: 35,176,485	intron	c.68-90A>G	.
	Chr. 11: 35,200,315	intron	c.923-767T>A *	.
	Chr. 11: 35,201,611	intron	c.1037-60T>C *	.
	Chr. 11: 35,204,608	missense	c.1250A>G *	p.Lys417Arg
	Chr. 11: 35,208,126	missense	c.1436T>C *	p.Ile479Thr
	Chr. 11: 35,222,497	3_prime_UTR	c.*119G>C *	.
	Chr. 11: 35,222,511	3_prime_UTR	c.*133A>G*	.
14	Chr. 11: 35,200,315	intron	c.923-767T>A *	.
	Chr. 11: 35,201,611	intron	c.1037-60T>C *	.

Table S3. Mutations identified in *CD44* gene, chromosome position, mutation type, nucleotide change, amino acid change (continued).

Patient no.	Chromosome position	Mutation type	Nucleotide change	Amino acid change
14	Chr. 11: 35,204,608	missense	c.1250A>G *	p.Lys417Arg
	Chr. 11: 35,208,126	missense	c.1436T>C *	p.Ile479Thr
	Chr. 11: 35,222,497	3_prime_UTR	c.*119G>C *	.
	Chr. 11: 35,222,511	3_prime_UTR	c.*133A>G*	.
22	Chr. 11: 35,176,485	intron	c.68-90A>G	.
	Chr. 11: 35,200,315	intron	c.923-767T>A *	.
	Chr. 11: 35,201,611	intron	c.1037-60T>C *	.
	Chr. 11: 35,204,608	missense	c.1250A>G *	p.Lys417Arg
	Chr. 11: 35,208,126	missense	c.1436T>C *	p.Ile479Thr
	Chr. 11: 35,222,497	3_prime_UTR	c.*119G>C *	.
	Chr. 11: 35,222,511	3_prime_UTR	c.*133A>G *	.
23	Chr. 11: 35,150,575	intron	c.67+11205G>A	.
	Chr. 11: 35,153,498	intron	c.67+14128T>C	.
	Chr. 11: 35,176,485	intron	c.68-90A>G	.
	Chr. 11: 35,200,315	intron	c.923-767T>A *	.
	Chr. 11: 35,201,611	intron	c.1037-60T>C *	.
	Chr. 11: 35,204,608	missense	c.1250A>G *	p.Lys417Arg
	Chr. 11: 35,208,126	missense	c.1436T>C *	p.Ile479Thr
	Chr. 11: 35,222,497	3_prime_UTR	c.*119G>C *	.
	Chr. 11: 35,222,511	3_prime_UTR	c.*133A>G *	.
24	Chr. 11: 35,150,575	intron	c.67+11205G>A	.
	Chr. 11: 35,153,498	intron	c.67+14128T>C	.
	Chr. 11: 35,162,980	intron	c.68-13595C>T	.
	Chr. 11: 35,171,082	intron	c.68-5493C>T	.
	Chr. 11: 35,176,485	intron	c.68-90A>G	.
	Chr. 11: 35,176,561	intron	c.68-14A>G	.
	Chr. 11: 35,200,315	intron	c.923-767T>A *	.
	Chr. 11: 35,200,358	intron	c.923-724G>A	.
	Chr. 11: 35,201,611	intron	c.1037-60T>C *	.
	Chr. 11: 35,204,608	missense	c.1250A>G *	p.Lys417Arg
	Chr. 11: 35,208,126	missense	c.1436T>C *	p.Ile479Thr
	Chr. 11: 35,219,242	intron	c.1874-74T>A	.
	Chr. 11: 35,222,497	3_prime_UTR	c.*119G>C *	.
	Chr. 11: 35,222,511	3_prime_UTR	c.*133A>G *	.

*** Mutations found in all 12 patients.**

Table S4. Pearson correlation coefficients among study variables in PV patients.

	Age	Gender	WBC	Hemoglobin	Platelet counts	LW/ICAM (CD242)	Indian (CD44)	Lutheran/ BCAM (CD239)	Rh-related IAP (CD47)	*JAK2*-MRD
Age	-									
Gender	0.046	-								
WBC	0.026	0.017	-							
Hemoglobin	-0.130	0.217	-0.020	-						
Platelet counts	-0.408 **	-0.110	0.123	-0.379 **	-					
LW/ICAM (CD242)	0.183	-0.026	0.005	-0.219	-0.022	-				
Indian (CD44)	0.197	0.108	0.208	0.007	0.040	0.475 **	-			
Lutheran/BCAM (CD239)	0.237	0.180	0.266	-0.312 *	0.098	0.211	0.166	-		
Rh-related IAP (CD47)	0.095	0.023	0.248	-0.030	0.070	0.162	0.624 **	0.142	-	
***JAK2*-MRD**	0.100	-0.109	0.402 *	-0.246	0.230	0.341	0.247	0.028	0.242	-

Significant correlations are denoted with asterisks at significance level, * p-value < 0.05 and ** p-value < 0.01 in underlined line numbers.