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Predictive accuracy of the low erythropoietin level for the diagnosis of Polycythemia Vera

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Hematology and Oncology Devision

Henry Ford Cancer Institute

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PV

- First described in 1892
- Incidence of at least 2 per 100 000
- 10 decades of investigation - the etiology and pathophysiology of polycythemia vera still not fully understood
- **William Osler** was the first to emphasize that phenotypic mimicry could confound the diagnostic process
  - Proposed clinical criteria to distinguish polycythemia vera from other disorders causing erythrocytosis

The diagnosis of polycythemia vera

1903*	1971†
Erythrocytosis Cyanosis Splenomegaly	Elevated red cell mass Normal arterial O_2 saturation Splenomegaly Plus any 2 below if no splenomegaly Leukocytosis greater than 12 000/μL Thrombocytosis greater than 400 000/μL Leukocyte alkaline phosphatase greater than 100 Serum B_{12} greater than 900 pg/mL or unbound B_{12} binding capacity greater than 2200 pg/mL

* From Osler.71

† From Wasserman.72

Evolution of Diagnostic Criteria

WHO 2008 Diagnostic Criteria for PV

Stratification of Criteria	Clinical and Laboratory Features
Major criteria	Hgb >18.5* g/dL (men) Hgb >16.5 g/dL* (women) ***or*** presence of *JAK2 V617F* or *JAK2* exon 12 mutation
Minor criteria	BM trilineage myeloproliferation Subnormal serum erythropoietin level EEC growth

- Patients must meet:
  - Both major criteria and 1 minor criterion ***or***
  - The first major criteria and 2 minor criteria

*Lindsey Lyle inadvertently stated these as hematocrit values.

Swerdlow SH, et al. *WHO Classification of Tumours of Haemopoietic and Lymphoid Tissues.* 2008.

WHO 2016 Diagnostic Criteria for PV

Stratification of Criteria	Clinical and Laboratory Features
Major criteria	1. HGB >16.5 g/dL (men), >16.0 g/dL (women) ***OR*** HCT >49% (men), >48% (women) ***OR*** increased red cell mass 2. BM biopsy showing hypercellularity for age with trilineage growth, including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes 3. Presence of *JAK2 V617F* or *JAK2* exon 12 mutation
Minor criterion	• Subnormal serum EPO level

- Patients must meet either all 3 major criteria ***or*** the first 2 major criteria and the minor criterion

Arber DA, et al. *Blood.* 2016;127:2391-2405.

Due to the unique physiology of erythropoietin, measurement of the hormone in the circulation cannot be relied on to distinguish between autonomous and erythropoietin-driven erythrocytosis

The diagnostic value of EPO has been debated due to the increasing availability of advanced molecular testing

We hypothesized that EPO level may not provide additional diagnostic information

Methods

- Retrospective chart review 415 patient records were reviewed.
- 161 patients had erythropoietin values checked in their EMRs.
- 23 of the 161 patients have diagnosis date missing or JAK2V617F mutation status missing.
- 138 patients included in final analysis
- Logistic regression was used to build a predictive model for the diagnosis of PV based on EPO value and JAK2V617F mutation status.
  - A weakly informative prior was used when there is complete separation in logistic regression.
- The area under the receiver operating characteristic curve (AUC) was calculated to evaluate the predictive accuracy.
- A p-value less than 0.05 was considered statistically significant.

The main clinical and hematological characteristics
Table 1

		All		PV		no PV		
	Group	Frequency	%	Frequency	%	Frequency	%	P
Gender	Female	63	45.7	42	56	21	33.3	0.013
	Male	75	54.3	33	44	42	66.7	
Race	WH	101	73.2	49	65.3	52	82.5	0.065
	BA	28	20.3	19	25.3	9	14.3	
	OTH	9	6.5	7	9.3	2	3.2	
Smoking Status	Never	38	27.5	32	42.7	6	9.5	<0.001
	Current	23	16.7	4	5.3	19	30.2	
	Former	74	53.6	37	49.3	37	58.7	
	Missing	3	2.2	2	2.7	1	1.6	
BMI	Normal	42	31.8	30	41.1	12	20.3	0.009
	Overweight	44	33.3	25	34.2	19	32.2	
	Obese	46	34.8	18	24.7	28	47.5	
JAK2axon12	N	48	35	19	25.7	29	46	0.014
	P	2	1.5	2	2.7	0	0	
	na	87	63.5	53	71.6	34	54	
BM.bx	Y	44	32.1	33	44	11	17.7	0.002
	na	93	67.9	42	56	51	82.3	

Results

Table 2

PPV and NPV of suboptimal EPO level

		PV	No PV	
Erythropoietin Level	‹ 3.7 mU/mL	51	4	PPV 92.7%
	› 3.7 mU/mL	24	59	NPV 71.1%
		Sensitivity 68%	Specificity 93.7%	

Table 3

The correlation of erythropoietin value with other variables

	Rho	P-value
BMI	0.33	<0.001
Age	-0.07	0.43
Hb	-0.16	0.053
Hct	-0.3	<0.001
WBC	-0.33	<0.001
Plts	-0.56	<0.001
GFR	-0.09	0.28
Cr	0.18	0.032

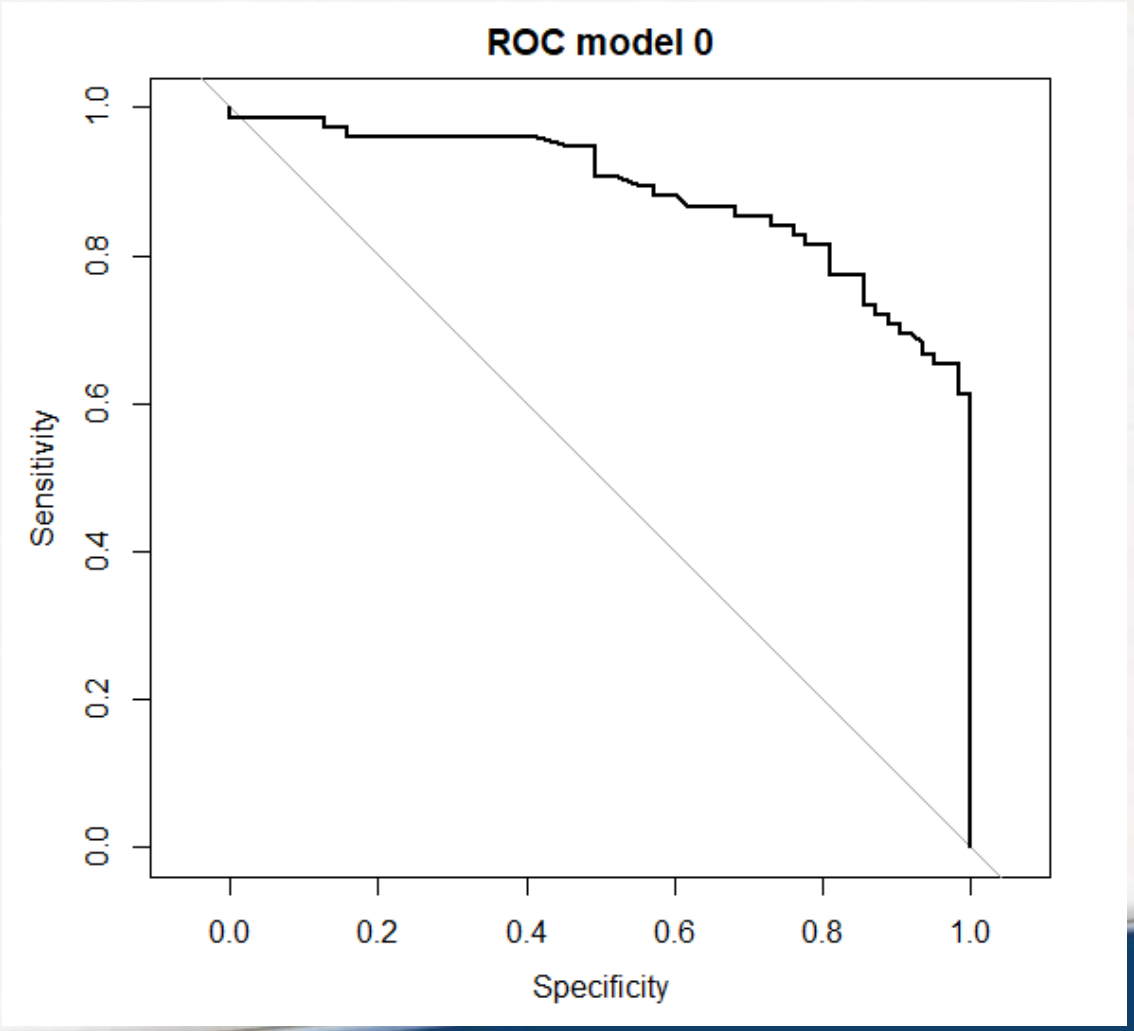
Model zero

When we only include erythropoietin in the model (model 0), it is significantly associated with PV

OR 0.857; p-value <0.001,

AUC for the model zero is 0.8841

Used for comparative purpose



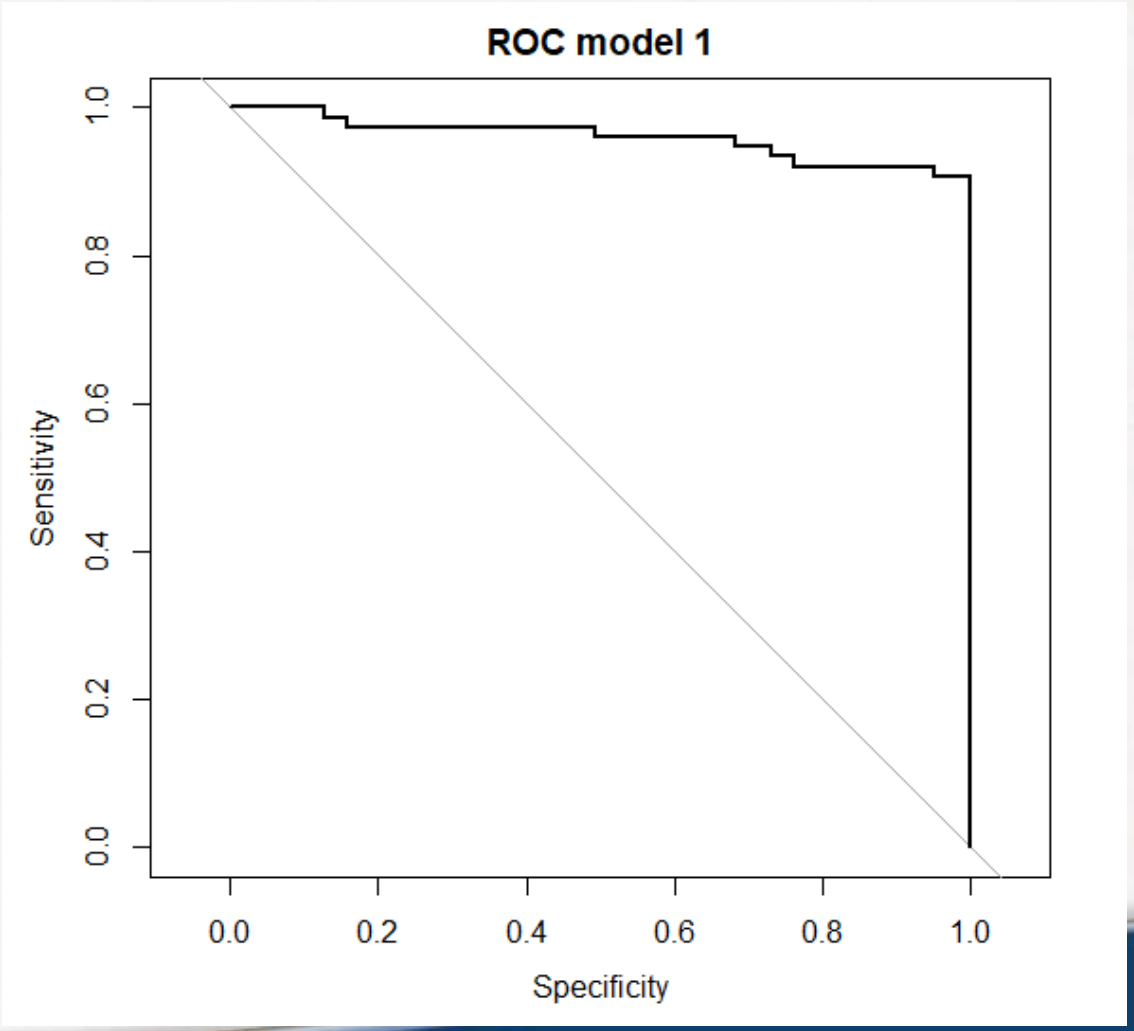
Model 1

Predictive value of suboptimal erythropoietin level and JAK2 V617F mutation status

Erythropoietin level is not significantly associated with the diagnosis of PV

OR 0.960, p-value 0.314

Model 1 give an AUC 0.9587

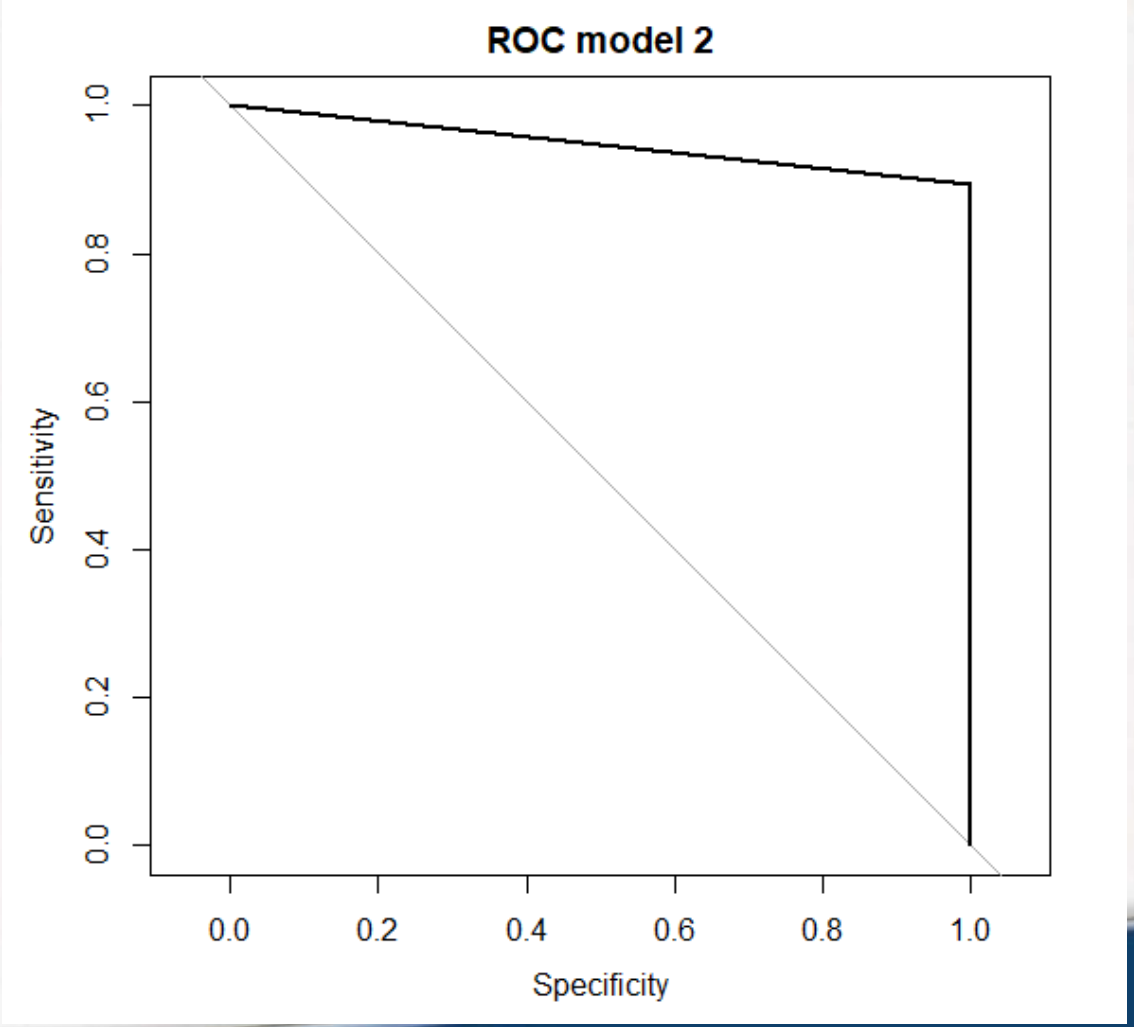


Model 2

Model 2 shows the predictive value of the JAK2 V617F for the diagnosis of the PV alone

OR 2142.7; p<0.001

AUC is 0.9467.



Discussion

- Results show that erythropoietin level below the normal range does not bring additional diagnostic value when JAK2V617F mutation status is positive.
- Additionally, erythropoietin level has a negative correlation with increased BMI and smoking status, making not reliable diagnostic marker.
- The utility of EPO in differentiating between primary and secondary erythrocytosis is largely based on early trials prior to the discovery of JAK2.
- Potential limitations of the study include intrinsic bias of retrospective analysis, inability to standardize bone marrow biopsy findings, incomplete records, and limited number of patients.
- Future direction