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Association between the CALLY index and thrombotic risk in polycythemia vera and essential thrombocythemia

Cumali Yalçın*, Can Özlü

Division of Hematology, Department of Internal Medicine, Faculty of Medicine, Kütahya Health Sciences University, Kütahya, Turkiye

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***Corresponding Author:** Cumali Yalçın, doktorcumali@hotmail.com

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ABSTRACT

Aims: Thrombotic complications are the leading cause of morbidity and mortality in patients with polycythemia vera (PV) and essential thrombocythemia (ET). The C-reactive protein–albumin–lymphocyte (CALLY) index has recently emerged as a biomarker reflecting systemic inflammation, nutritional status, and immune function. This study aimed to evaluate the association between the CALLY index and thrombotic risk in patients with PV and ET.

Methods: This retrospective single-center study included 96 adult patients diagnosed with PV or ET between 2015 and 2026. Clinical and laboratory data were obtained from hospital records. Thrombotic events present at diagnosis were confirmed using imaging methods. Receiver operating characteristic (ROC) analysis was performed to evaluate the discriminative ability of the CALLY index, and multivariate logistic regression analysis was used to identify independent factors associated with thrombosis.

Results: Among the patients, 77 (80.2%) had PV and 19 (19.8%) had ET. Thrombosis was detected in 27 patients. Patients with thrombosis had significantly lower CALLY scores compared to those without thrombosis (11.8±10.4 vs 19.2±18.9, p=0.010). Neutrophil counts were significantly higher in the thrombosis group (p=0.014). Lymphocyte counts were significantly lower in patients with thrombosis compared to those without thrombosis (p=0.016). ROC analysis demonstrated moderate discriminative ability for thrombosis (AUC: 0.670, 95% confidence interval (CI): 0.543–0.788). In multivariate analysis, a low CALLY index (<12) was independently associated with thrombosis (odds ratio (OR): 4.33, 95% CI: 1.54–12.15, p=0.015).

Conclusion: The lower CALLY index may represent a simple and clinically supportive biomarker for thrombotic risk assessment in PV and ET patients.

Keywords: Biomarkers, essential thrombocythemia, polycythemia vera, thrombosis

INTRODUCTION

Polycythemia vera (PV) and essential thrombocythemia (ET) are classic myeloproliferative neoplasms (MPNs) with the potential to progress to myelofibrosis or acute leukemia.[1] Across this disease spectrum, thromboembolic complications stand out as the foremost contributor to morbidity and death.[2] In recent years, the C-reactive protein–albumin–lymphocyte (CALLY) index—a single metric that captures systemic inflammation, nutritional state, and host immunity—has attracted growing interest as a practical, low-cost laboratory tool.[3,4]

The CALLY index integrates C-reaktif protein (CRP) as a marker of inflammation, albumin as an indicator of nutritional status, and lymphocyte count as a key component of immune function into a single scoring system.[5] This index has been shown to serve as an important prognostic value not only in various oncological conditions, including colorectal cancer, hepatocellular carcinoma, renal cell carcinoma, and esophageal cancer, but also in cardiovascular diseases.[6–9]

Among hematologic malignancies, recent studies—particularly in primary myelofibrosis (PMF)—have demonstrated that the CALLY index may have prognostic potential in specific clinical subgroups of patients with prior thrombosis.[10] Yet whether this index meaningfully stratifies thrombotic risk in PV and ET has not been adequately addressed. Therefore, the aim of the present study is to evaluate the association between the CALLY index at diagnosis and vascular complications in PV and ET patients.

METHODS

This study was approved by the Non-interventional Clinical Researches Ethics Committee of Kütahya Health Sciences University (Date: 09.03.2026, Decision No: 2026/03-43). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Designed as a single-center retrospective observational study, this research enrolled adult patients diagnosed with

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PV or ET at the Kütahya Health Sciences University Kütahya City Hospital's Hematology Clinic between January 2015 to February 2026. Demographic characteristics, clinical findings, and laboratory parameters were recorded for all patients from patient files and hospital information systems. Baseline CALLY scores were derived from laboratory values obtained at the time of diagnosis using the formula below.[11]

CALLY index=albumin level (g/dl)×lymphocyte count (/μL)/ CRP level (mg/dl)x10^4

As laboratory parameters in our institution are routinely reported in SI units, the formula was adapted accordingly as: CALLY index=Albumin (g/L)×Lymphocyte count (×10^9/L)/ CRP (mg/L). The criteria for thrombotic events included arterial or venous thrombosis located in the cerebral, coronary, pulmonary, abdominal, or peripheral vascular systems. All events required radiological confirmation via computed tomography (CT), magnetic resonance imaging (MRI), or Doppler ultrasonography.

Statistical Analysis

All analyses were conducted with IBM SPSS Statistics (version 26.0; IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean±standard deviation and categorical variables as frequencies with percentages. Group comparisons for continuous measures used the Mann–Whitney U test, selected on the basis of distributional properties; categorical variables were compared with the chi-square test. The ability of the CALLY index to discriminate thrombosis was evaluated using ROC curve analysis. To identify independent risk factors, we built a multivariate logistic regression model incorporating variables that reached p<0.05 in univariate testing. A two-tailed p value below 0.05 was considered statistically significant throughout.

Table 1. Demographics and clinical characteristics of patients(n=96)

Variables	All patients (n=96), %
Gender, male (%)	60 (62.5)
PV	77 (80.2)
ET	19 (19.8)
JAK2 V617F (+)	82 (85.4)
Splenomegaly (+)	47 (49.0)
B symptoms (+)	22 (22.9)
ECOG 0	62 (64.6)
ECOG 1	24 (25.0)
ECOG 2	7 (7.3)
ECOG 3	3 (3.1)
Myelofibrotic Transformation	8 (8.3)
Survival, exitus	1 (1.0)
	Mean±SD
Age (year)	62.1±14.5
Albumin (g/L)	44.2±2.7
Hgb (g/dl)	16.9±1.8
Hct (%)	50.2±6.5
WBC (×10^9/L)	11.2±4.2
Neutrophil count (×10^9/L)	7.8±3.6
Lymphocyte count (×10^9/L)	2.3±0.8
Monocyte (×10^9/L)	0.7±0.4
Platelet (×10^9/L)	516±284
MPV	9.9±1.1
LDH	251.2±78.4
CRP (mg/L)	9.47±7.01
CALLY index	12.6±18.5

PV: Polycythemia vera, ET: Essential thrombocythemia, JAK2 V617F: Janus kinase 2 V617F mutation, ECOG: Eastern Cooperative Oncology Group, SD: Standard deviation, Hct: Hematocrit, Hgb: Hemoglobin, WBC: White blood cell, MPV: Mean platelet volume, LDH: Lactate dehydrogenase, CRP: C-reactive protein, CALLY: C-reactive protein-Albumin-Lymphocyte index

RESULTS

Ninety-six patients with PV or ET formed the study population. Males predominated (62.5%), and diagnosed with PV (80.2%), while 19.8% had ET. The Janus kinase 2 V617F mutation (JAK2 V617F) mutation was present in 85.4% of patients. Splenomegaly and B symptoms were observed in 49.0% and 22.9% of patients, respectively. Performance status was generally preserved, with 64.6% achieving Eastern Cooperative Oncology Group (ECOG) 0. During follow-up, myelofibrotic transformation occurred in 8.3% of patients, while only one death (1.0%) was recorded. The mean age of the patients was 62.1±14.5 years. Laboratory parameters were consistent with the underlying myeloproliferative phenotype, with elevated hemoglobin, hematocrit, and platelet levels. The mean CALLY index was 12.6±18.5 (**Table 1**). The median follow-up duration was 36 months (range, 10–125 months).

Thrombosis was documented in 27 patients (29%), occurring either at diagnosis (n=8) or following diagnosis (n=19). Arterial thrombosis was observed in 20 patients, including coronary artery thrombosis in 14, cerebrovascular events in 5, and peripheral artery thrombosis in 1. Venous thrombosis was present in 7 patients, comprising deep vein thrombosis in 5, pulmonary embolism in 1, and superficial thrombophlebitis in 1. Comparing the two groups, we found no meaningful differences in age, gender, diagnosis subtype, splenomegaly, B symptoms, ECOG score, JAK2 status, or myelofibrotic transformation (all p>0.05). On the laboratory side, neutrophil count stood out as significantly elevated in thrombotic patients (8.9±3.4 vs 7.5±3.6×10^9/L, p=0.014), while lymphocyte counts were lower in this group (p=0.016). Other hematologic variables, including hemoglobin, hematocrit, white blood cell count, monocyte count, mean platelet volume (MPV), and lactate dehydrogenase (LDH), were comparable between the groups. Importantly, the CALLY index was significantly lower among thrombotic patients (11.8±10.4 vs 19.2±18.9, p=0.010), suggesting an inverse relationship between CALLY levels and thrombotic risk (**Table 2**).

ROC analysis demonstrated that the CALLY index had a modest discriminative ability in identifying thrombosis, with an area under the curve (AUC) of 0.670 (95% confidence interval (CI): 0.543–0.788). The optimal cut-off value was identified as 12.0 using the Youden index, yielding a sensitivity of 74.1% and a specificity of 62.3% (**Figure**).

Variables that were significantly associated with thrombosis in univariate analyses, including the CALLY index (<12) and neutrophil and lymphocyte count, were subsequently included in a multivariate analysis. Multivariate modeling showed that patients with a CALLY index <12 had a significantly higher risk of thrombosis (odds ratio (OR): 4.33, 95% CI: 1.54–12.15, p=0.015). Although neutrophil and

Table 2. Comparison of clinical, hematologic, and inflammatory indices between patients with and without thrombosis

Variable	Thrombosis (+) n=27	Thrombosis (-) n=69	p value
Age (year)	63.5±13.5	61.3±15.0	0.496
Albumin (g/L)	44.0±3.1	44.3±2.5	0.793
Hgb (g/dl)	17.3±1.0	16.7±2.1	0.367
Hct (%)	51.1±6.7	49.8±6.4	0.249
WBC ($\times10^9$/L)	11.6±3.7	11.0±4.4	0.357
Neutrophil count ($\times10^9$/L)	8.9±3.4	7.5±3.6	0.014
Lymphocyte count ($\times10^9$/L)	2.2±0.8	2.5±0.7	0.016
Monocyte ($\times10^9$/L)	0.7±0.6	0.7±0.3	0.257
MPV	10.0±1.3	9.8±1.0	0.607
LDH	254.3±77.9	250.0±79.1	0.867
CRP (mg/L)	8.81±6.83	9.44±5.77	0.650
CALLY index	11.8±10.4	19.2±18.9	0.010
ECOG 0	17 (63.0)	45 (65.2)	0.854
ECOG 1	7 (25.9)	17 (24.6)	0.901
ECOG 2	3 (11.1)	4 (5.8)	0.643
ECOG 3	0 (0.0)	3 (4.3)	0.654
JAK2 V617F (+)	25 (92.6)	57 (82.6)	0.223
Myelofibrotic Transformation	4 (14.8)	4 (5.8)	0.305
Splenomegaly (+)	15 (55.6)	32 (46.4)	0.592
B symptoms (+)	9 (33.3)	13 (18.8)	0.184
Death	1 (3.7)	0 (0.0)	0.625

Hgb: Hemoglobin, Hct: Hematocrit, WBC: White blood cell, MPV: Mean platelet volume, LDH: Lactate dehydrogenase, C-reactive protein, CALLY: C-reactive protein–albumin–lymphocyte index, ECOG: Eastern Cooperative Oncology Group, JAK2 V617F: Janus kinase 2 V617F mutation

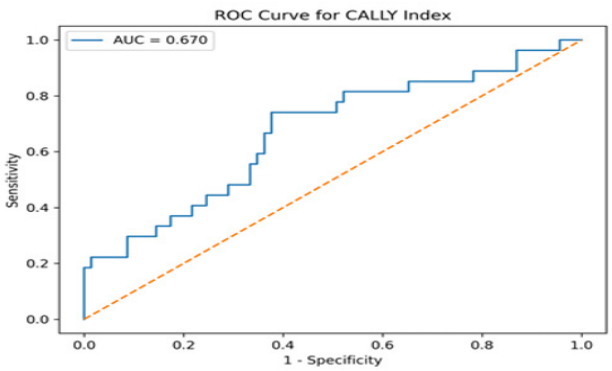


Figure. ROC curve analysis for thrombosis discrimination using the CALLY index. The area under the curve was 0.670 (95% CI, 0.543–0.788), and the optimal cut-off value determined by the Youden index was 12.0, with a sensitivity of 74.1% and a specificity of 62.3%.

lymphocyte counts did not retain independent statistical significance, the associations between neutrophils and thrombosis remained notable (**Table 3**).

Table 3. Multivariate logistic regression analysis for thrombosis

Variable	OR	95% CI	p value
CALLY <12	4.33	1.54 – 12.15	0.015
Neutrophil	1.12	0.99 – 1.28	0.069
Lymphocyte	1.36	0.75 – 2.46	0.312
		Nagelkerke R^2 = 0.165	

OR: Odds ratio, CI: Confidence interval, CALLY: C-reactive protein–albumin–lymphocyte index

DISCUSSION

This study evaluated the association between the CALLY index and the occurrence of thrombotic complications in cohorts of PV and ET patients. We found that a low CALLY index (<12) was associated with a substantially higher risk of thrombosis and remained an independent risk factor in this patient population. Given the multifactorial nature of thrombogenesis in myeloproliferative neoplasms, our results support the potential utility of composite biomarkers such as the CALLY index in improving risk stratification and identifying patients at higher risk for vascular complications.

Thrombosis drives much of the morbidity and mortality burden in PV and ET. While traditional risk stratification systems rely primarily on age and thrombosis history, increasing evidence suggests that chronic inflammation and immune dysregulation play central roles in MPN-associated thrombogenesis.[12] Inflammatory cytokine release promotes vascular events by contributing to endothelial dysfunction, platelet activation, leukocyte adhesion, and hypercoagulation. Recent studies have highlighted thromboinflammation as a feature of MPN biology and may represent a significant therapeutic target.[13,14]

The CALLY index combines CRP, albumin, and lymphocyte count in a single biomarker reflecting systemic inflammation, nutritional status, and host immune capacity.[15,16] Therefore, a low CALLY score may indicate a pro-inflammatory and immunologically disrupted microenvironment that supports the development of thrombosis. In our cohort, patients with thrombosis had significantly lower CALLY scores than those without thrombosis, supporting the hypothesis that inflammatory and immune-mediated mechanisms significantly contribute to vascular complications in PV and ET.

Other inflammation-based composite indices—the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), and HALP score—have each been linked to thrombosis and poor outcomes in MPN populations.[17-19] Similar to these indices, the CALLY index appears to capture multiple biological pathways simultaneously. Importantly, unlike isolated inflammatory markers, the CALLY index combines inflammatory, nutritional, and immune parameters, potentially enhancing its prognostic utility in chronic inflammatory malignancies such as MPNs.

Another important finding of our study is the association between high neutrophil count and thrombosis. Although the neutrophil count did not retain statistical significance in the multivariate analysis, neutrophils are increasingly recognized as active mediators of thrombosis. This involvement is primarily driven by the formation of neutrophil extracellular traps (NETs), endothelial activation, and complex interactions with platelets. Experimental and translational studies have shown increased NETosis in MPN patients, particularly in JAK2 mutation disease, supporting the mechanistic role of neutrophils in MPN-associated thrombosis.[20-22]

ROC analysis showed that the CALLY index has moderate discriminatory performance in thrombotic risk, with an AUC of 0.670. Although this discriminative ability is modest, its relatively high sensitivity suggests that the CALLY index

could be used as a practical biomarker in daily clinical practice. Since CRP, albumin, and lymphocyte counts are routinely obtainable laboratory parameters, the CALLY index can be easily calculated without additional cost or the need for specialized testing. Nevertheless, the cut-off value of 12.0 identified in the present study was derived from a single-center retrospective cohort with a relatively small sample size, and its performance may not be generalizable to other populations. Therefore, this cut-off should be regarded as exploratory, and prospective, multicenter studies with external validation are needed before it can be recommended for routine clinical decision-making.

Limitations

This study has several limitations. First, the retrospective, single-center design may lead to selection bias. The relatively small sample size may have limited statistical power and prevented the detection of weaker associations. The limited number of ET patients and associated thrombotic events precluded a separate subgroup analysis due to the risk of statistical insufficiency and unreliable estimates. Consequently, our findings predominantly reflect the PV population, and their generalizability to ET patients is limited. In the present study, we used a multivariate logistic regression model including variables associated with thrombosis in univariate analysis, while also considering the limited number of thrombotic events to avoid model overfitting. Since lymphocyte count is a component of the CALLY index, the simultaneous inclusion of both variables in the multivariable model raises the possibility of multicollinearity, which could inflate the variance of the regression estimates and affect the stability of the odds ratios obtained. Due to data unavailability, known risk factors for PV and ET, such as cardiovascular risk factors (e.g., smoking, hypertension, diabetes mellitus, hyperlipidemia), treatment status, and hematocrit control, could not be evaluated. Arterial and venous thrombotic events were not analyzed separately. Additionally, thrombotic events present at diagnosis and those occurring during follow-up were analyzed together. Although all events were objectively confirmed, this approach may have introduced clinical heterogeneity because baseline and incident thrombotic events may reflect different underlying disease characteristics and risk profiles. Finally, the CALLY was assessed based on a single measurement at diagnosis; dynamic changes were not monitored.

CONCLUSION

Our findings demonstrate that a low CALLY index is independently associated with increased thrombotic risk in PV and ET patients. The CALLY index could be a simple, inexpensive, and clinically supportive biomarker reflecting the underlying inflammatory and immune mechanisms of thrombosis in MPNs. Furthermore, future prospective studies involving larger and more balanced PV and ET patient cohorts are needed to confirm the association separately for each disease subtype.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was approved by the Non-interventional Clinical Researches Ethics Committee of Kütahya Health Sciences University (Date: 09.03.2026, Decision No: 2026/03-43).

Informed Consent

This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

Concept: CY; Design: CY; Control: CÖ; Resources: CÖ, CY; Materials: CY, CÖ; Data Collection and/or Processing: CY, CÖ; Analysis and/or Interpretation: CÖ, CY; Literature Review: CÖ; Writing The Article: CY; Critical Review: CY, CÖ.

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