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Hematological, Coagulation, and Oxidative Stress Profiles in Patients with Polycythemia Vera and Concomitant Metabolic Syndrome: A Comparative Cross-Sectional Study

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Abstract

In this cross-sectional comparative study, 169 participants were enrolled and classified into four groups: healthy controls ($n = 53$), PV ($n = 30$), MetS ($n = 50$), and PV+MetS ($n = 36$). Hematological, biochemical, coagulation, and oxidative stress parameters were analyzed. Total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) were determined using automated colorimetric methods. Platelet mass index (PMI) was calculated as platelet count × mean platelet volume. Receiver operating characteristic (ROC) curve and Pearson correlation analyses were performed to assess diagnostic performance and associations among laboratory parameters. Significant intergroup differences were observed in platelet count ($p = 0.0001$), PMI ($p = 0.0007$), D-dimer ($p = 0.001$), urea ($p = 0.0003$), creatinine ($p = 0.016$), total bilirubin ($p = 0.0001$), gamma-glutamyl transferase ($p = 0.005$), magnesium ($p = 0.0075$), lactate dehydrogenase (LDH) ($p < 0.0001$), copper ($p = 0.01$), zinc ($p = 0.01$), TAS ($p < 0.0001$), and OSI ($p < 0.0001$). Platelet counts were significantly higher in the PV group than in controls and in the PV+MetS group than in the MetS group. D-dimer concentrations were highest in the PV+MetS group, indicating enhanced coagulation activation. TAS levels were significantly reduced, whereas TOS and OSI values were increased in patients with concomitant PV and MetS, suggesting impaired antioxidant defense and increased oxidative stress burden. ROC analysis demonstrated moderate discriminatory performance for D-dimer (AUC = 0.799), TAS (AUC = 0.774), LDH (AUC = 0.763), OSI (AUC = 0.750), and total bilirubin (AUC = 0.743). Correlation analysis revealed strong positive associations between platelet count and PMI (r = 0.97), ferritin and OSI (r = 0.82), and strong negative associations between TAS and OSI (r = −0.74). Concomitant PV and MetS were associated with increased platelet burden, higher D-dimer levels, reduced antioxidant capacity, and elevated oxidative stress markers. These findings suggest that platelet-related indices, D-dimer, LDH, TAS, and OSI may reflect exploratory laboratory alterations associated with the PV+MetS phenotype. However, because of the cross-sectional design and absence of thrombotic outcome data, prospective follow-up, treatment-adjusted analyses, and validation cohorts, these parameters should not be interpreted as validated tools for clinical risk stratification.

Keywords: polycythemia vera; metabolic syndrome; oxidative stress; hematology; coagulation; D-dimer; platelet mass index; ROC analysis

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1. Introduction

Polycythemia vera (PV) is a chronic myeloproliferative neoplasm characterized by clonal proliferation of hematopoietic stem cells and clinically manifests with erythrocytosis, leukocytosis, and thrombocytosis. PV is associated with an increased risk of arterial and venous thrombotic events, which remain major causes of morbidity and mortality in affected patients [1]. The pathogenesis of PV is strongly linked to constitutive activation of the JAK–STAT signaling pathway, most commonly due to JAK2 mutations. In addition to uncontrolled hematopoietic proliferation, JAK2-driven signaling contributes to chronic inflammation, endothelial dysfunction, increased reactive oxygen species (ROS) production, genomic instability, and thromboinflammatory activation, thereby promoting vascular complications and disease progression [2,3].

Metabolic syndrome (MetS) is a multifactorial clinical condition characterized by central obesity, insulin resistance, dyslipidemia, hypertension, and impaired glucose metabolism. It is one of the most prevalent metabolic disorders worldwide and represents a major contributor to cardiovascular morbidity and mortality [4]. Chronic low-grade inflammation, oxidative stress, endothelial dysfunction, and activation of coagulation pathways are central mechanisms linking MetS to cardiovascular disease and vascular dysfunction [5–7].

Although PV and MetS arise from distinct primary pathogenic mechanisms, both conditions are associated with proinflammatory, prothrombotic, and oxidative stress-related biological responses. Their coexistence may therefore be better understood as an overlap of converging downstream pathways rather than a shared disease-specific mechanism. These pathways include platelet activation, cytokine imbalance, endothelial dysfunction, redox imbalance, and coagulation pathway activation [8,9]. When present together, PV and MetS may be associated with overlapping thromboinflammatory and redox-related laboratory alterations; however, formal interaction or additivity cannot be inferred without dedicated statistical testing.

Emerging evidence suggests that metabolic abnormalities may influence disease burden, inflammatory activity, and thrombotic risk in patients with myeloproliferative neoplasms. Previous studies have reported an increased prevalence of MetS among patients with myeloproliferative disorders compared with the general population, and this coexistence may further contribute to cardiovascular complications and thrombosis [10]. Therefore, evaluating the biological consequences of MetS in patients with PV may help characterize laboratory phenotypes and generate hypotheses for future outcome-based studies.

Oxidative stress represents an important mechanistic link between metabolic dysregulation, inflammation, endothelial dysfunction, and thrombosis. It results from an imbalance between excessive ROS generation and insufficient antioxidant defense capacity [11]. Excessive ROS production promotes lipid peroxidation, protein oxidation, DNA damage, and activation of proinflammatory pathways, ultimately contributing to endothelial injury and vascular dysfunction [12]. In MetS, insulin resistance, hyperglycemia, dyslipidemia, mitochondrial dysfunction, and advanced glycation end-product formation contribute to sustained oxidative stress and chronic inflammation [7,13]. Similarly, in PV, JAK2-mediated signaling, increased cellular turnover, leukocyte activation, and inflammatory cytokine release may increase oxidative burden. These mechanisms suggest that concomitant PV and MetS may be associated with a cumulative impairment in redox balance.

Platelet-related biomarkers may provide additional insight into this laboratory phenotype. Platelet mass index (PMI), which integrates platelet count and mean platelet volume, has been proposed as a potential indicator of platelet-related laboratory burden. In addition, coagulation and oxidative stress markers may help characterize the biological phenotype associated with PV, MetS, and their coexistence. In the present study, we evalu-

ated whether patients with concomitant PV and MetS demonstrate distinct hematological, coagulation-related, biochemical, and oxidative stress profiles compared with patients with either condition alone and healthy controls.

Although the individual effects of PV and MetS have been investigated separately, limited information is available regarding their combined impact on hematological, biochemical, coagulation, and oxidative stress parameters. We hypothesized that patients with concomitant PV and MetS would exhibit a distinct biological profile characterized by enhanced thromboinflammatory activity and impaired redox balance compared with patients with either condition alone and healthy controls. Therefore, this study aimed to evaluate hematological, biochemical, coagulation, and oxidative stress parameters in patients with PV, MetS, and concomitant PV+MetS and to compare these findings with those of healthy controls.

2. Materials and Methods

This cross-sectional comparative study was conducted in accordance with the Declaration of Helsinki and approved by the Harran University Clinical Research Ethics Committee (Approval No: HRU/23.24.13). The study was performed between 2023 and 2026, and blood samples were collected between 2024 and 2025 from patients followed in the Hematology Department of Şanlıurfa Mehmet Akif İnan Training and Research Hospital. A total of 169 individuals were enrolled and classified into four groups: patients with polycythemia vera (PV) ($n = 30$), patients with metabolic syndrome (MetS) ($n = 50$), patients with concomitant PV and MetS (PV+MetS) ($n = 36$), and age- and sex-matched healthy controls ($n = 53$).

The diagnosis of PV was established according to the World Health Organization (WHO) criteria, whereas MetS was defined according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria [14]. MetS was diagnosed in the presence of at least three of the following components: abdominal obesity, hypertriglyceridemia, reduced high-density lipoprotein (HDL) cholesterol, hypertension, and impaired fasting glucose. Only participants aged 18 years or older were included in the study.

To minimize potential confounding effects on inflammatory and oxidative stress-related parameters, individuals with acute infection, active malignancy other than PV, severe hepatic or renal insufficiency, a history of blood transfusion within the previous three months, or current use of antioxidant supplementation or antioxidant therapy were excluded. Since metabolic syndrome is frequently associated with chronic low-grade inflammation related to obesity, hypertension, and type 2 diabetes mellitus, these comorbidities were not considered exclusion criteria unless accompanied by an acute inflammatory process or clinically significant systemic inflammatory disease.

Information regarding hydroxyurea therapy, phlebotomy history, low-dose aspirin use, disease duration, smoking status, and concomitant cardiometabolic medications was obtained from patient medical records when available. These variables were summarized descriptively and considered potential confounders. Because of the limited sample size, treatment heterogeneity, and absence of thrombotic outcome data, treatment-adjusted multivariable models and treatment-specific subgroup analyses were not performed.

Venous blood samples were obtained from all participants following an overnight fasting period of 8–12 h. To minimize circadian variation, all samples were collected during the morning hours. Blood samples were processed within one hour after collection. Serum samples were separated by centrifugation at 3000 rpm for 10 min and stored at −80 °C until analysis.

Hematological parameters, including red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), white blood cell count (WBC), platelet count (PLT), and mean platelet volume (MPV), were measured using a Sysmex XN-2000 hematology analyzer (Sysmex Inc., Kobe, Japan). PMI was calculated as platelet count × mean platelet volume. Biochemical analyses included glucose, urea, creatinine, total bilirubin, gamma-glutamyl transferase (GGT), magnesium, lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, copper, zinc, and D-dimer measurements. All biochemical parameters were analyzed using a Roche Cobas 6000 c autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's instructions. Total antioxidant status (TAS) and total oxidant status (TOS) were measured using the fully automated colorimetric methods developed by Erel [15]. The oxidative stress index (OSI), representing the overall oxidant-antioxidant balance, was calculated as the ratio of TOS to TAS.

Statistical Analysis

Statistical analyses were performed using GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA). Data distribution was assessed using the Shapiro–Wilk normality test. Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were presented as frequencies and percentages.

Comparisons among the four study groups were performed using one-way analysis of variance (ANOVA) for normally distributed continuous variables and the Kruskal–Wallis test for non-normally distributed continuous variables. When a significant global difference was detected, pairwise post hoc comparisons were performed using Tukey's multiple-comparison test after ANOVA or Dunn's multiple-comparison test after Kruskal–Wallis analysis, thereby controlling for multiple pairwise testing within each parameter. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Unless otherwise specified, p values reported in the tables represent global four-group comparisons. Pairwise p values shown in the figures indicate selected post hoc comparisons among the study groups.

Receiver operating characteristic (ROC) curve analysis was performed as an exploratory analysis to evaluate the discriminatory performance of parameters demonstrating significant intergroup differences. The area under the curve (AUC), sensitivity, specificity, and optimal cut-off values were calculated using the Youden index. These ROC analyses were not intended to define diagnostic, prognostic, or clinical risk-stratification tools. Relationships between continuous variables were assessed using Pearson correlation analysis. All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

3. Results

A total of 30 patients with polycythemia vera (PV), 50 patients with metabolic syndrome (MetS), 36 patients with concomitant PV and MetS (PV+MetS), and 53 healthy controls were included in the study. Demographic and laboratory characteristics of the study groups are summarized in Table 1. No significant differences were observed among the groups regarding age, sex distribution, RBC count, hemoglobin, hematocrit, WBC count, glucose, CRP, ferritin, or TOS levels (all $p > 0.05$) (Table 1).

Clinical, cardiometabolic, and treatment-related variables that could potentially influence hematological, coagulation, and oxidative stress parameters are summarized in Table 2. BMI, diabetes mellitus, hypertension, statin use, antihypertensive use, antidiabetic medication, and aspirin use differed significantly among the groups, whereas current smoking did not. Among PV patients, hydroxyurea use and disease duration were similar between the PV and PV+MetS groups. These variables were interpreted descriptively as potential

confounders rather than as adjusted predictors because the study was not powered for treatment-adjusted or confounder-adjusted outcome modeling.

Table 1. Demographic, Hematological, Biochemical, Coagulation, and Oxidative Stress Characteristics of the Study Groups.

Parameter	Control (n = 53)	PV (n = 30)	MetS (n = 50)	PV+MetS (n = 36)	p Value *
Age (years)	61.6 ± 16.6	57.9 ± 19.9	49.6 ± 13.5	57.9 ± 19.9	>0.05
Male/Female	35/18	15/15	25/25	22/14	0.636
RBC ($\times 10^6/\mu L$)	5.0 ± 0.5	5.9 ± 0.8	5.1 ± 0.6	5.1 ± 1.2	>0.05
Hemoglobin (g/dL)	14.5 ± 1.6	17.2 ± 1.8	15.0 ± 1.7	15.1 ± 2.1	>0.05
Hematocrit (%)	42.1 ± 3.9	51.8 ± 5.2	44.6 ± 4.3	44.3 ± 6.5	>0.05
WBC ($\times 10^3/\mu L$)	8.3 ± 1.8	11.2 ± 3.8	8.7 ± 2.4	10.5 ± 8.0	>0.05
Platelets ($\times 10^3/\mu L$)	250.0 ± 61.2	363.0 ± 88.9	279.9 ± 141.5	378.2 ± 219.7	0.0001
MPV (fL)	10.3 ± 0.9	9.8 ± 0.9	10.0 ± 0.8	9.9 ± 0.8	0.026
PMI	2555 ± 574	3472 ± 1178	3381 ± 1466	3646 ± 2143	0.0007
Glucose (mg/dL)	91.8 ± 18.7	96.4 ± 18.5	128.6 ± 42.3	102.2 ± 38.7	>0.05
Urea (mg/dL)	23.8 ± 6.2	28.9 ± 10.4	27.5 ± 9.6	31.5 ± 12.9	0.0003
Creatinine (mg/dL)	0.76 ± 0.15	0.82 ± 0.19	0.79 ± 0.17	0.86 ± 0.26	0.016
Total bilirubin (mg/dL)	0.38 ± 0.19	0.72 ± 0.31	0.44 ± 0.20	0.64 ± 0.41	0.0001
GGT (U/L)	21.3 ± 11.9	28.4 ± 16.2	31.6 ± 21.8	34.2 ± 29.4	0.005
Magnesium (mg/dL)	2.20 ± 0.20	2.02 ± 0.18	2.05 ± 0.21	2.00 ± 0.20	0.0075
LDH (U/L)	170.6 ± 51.7	276.0 ± 108.0	192.0 ± 67.0	244.4 ± 99.9	<0.0001
CRP (mg/L)	2.6 ± 3.4	3.8 ± 4.5	4.6 ± 5.8	4.2 ± 5.1	>0.05
Copper (µg/dL)	122.5 ± 3.6	145.0 ± 18.0	142.0 ± 2.0	148.3 ± 10.9	0.01
Zinc (µg/dL)	128.0 ± 2.2	145.0 ± 35.0	136.0 ± 31.0	268.2 ± 66.6	0.01
D-dimer (mg/L)	0.25 ± 0.13	0.64 ± 0.41	0.38 ± 0.20	0.75 ± 0.97	0.001
Ferritin (ng/mL)	140.4 ± 256.0	102.0 ± 95.0	148.0 ± 17.0	125.6 ± 148.7	>0.05
TAS (mmol Trolox Eq/L)	11.1 ± 2.9	9.72 ± 3.03	10.09 ± 1.85	8.60 ± 2.00	<0.0001
TOS (µmol H_2O_2 Eq/L)	1.40 ± 0.30	0.93 ± 0.35	1.15 ± 0.42	1.50 ± 0.30	>0.05
OSI (AU)	0.0137 ± 0.0053	0.0103 ± 0.0047	0.0111 ± 0.0044	0.0185 ± 0.0062	<0.0001

Values are expressed as mean ± standard deviation (SD) or n (%), as appropriate. * p values represent global comparisons across the four study groups. Normally distributed continuous variables were analyzed using one-way ANOVA followed by Tukey's multiple-comparison test when appropriate; non-normally distributed variables were analyzed using the Kruskal–Wallis test followed by Dunn's multiple-comparison test when appropriate. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. Pairwise p values shown in the figures represent selected post hoc comparisons. Abbreviations: PV, polycythemia vera; MetS, metabolic syndrome; PMI, platelet mass index; MPV, mean platelet volume; LDH, lactate dehydrogenase; GGT, gamma-glutamyl transferase; TAS, total antioxidant status; TOS, total oxidant status; OSI, oxidative stress index.

Table 2. Clinical, Cardiometabolic, Treatment-Related, and Renal Function Variables Potentially Affecting Hematological, Coagulation, and Oxidative Stress Parameters.

Variable	Control (n = 53)	PV (n = 30)	MetS (n = 50)	PV+MetS (n = 36)	p Value
BMI, kg/m^2	24.7 ± 3.1	26.2 ± 4.2	31.4 ± 4.7	32.1 ± 5.1	<0.0001
Diabetes mellitus, n (%)	3 (5.7)	4 (13.3)	18 (36.0)	14 (38.9)	0.0001
Hypertension, n (%)	7 (13.2)	10 (33.3)	33 (66.0)	27 (75.0)	<0.0001
Current smoking, n (%)	11 (20.8)	9 (30.0)	13 (26.0)	11 (30.6)	0.707
Statin use, n (%)	4 (7.5)	5 (16.7)	19 (38.0)	15 (41.7)	0.0002
Antihypertensive use, n (%)	6 (11.3)	9 (30.0)	31 (62.0)	25 (69.4)	<0.0001
Antidiabetic medication, n (%)	2 (3.8)	3 (10.0)	17 (34.0)	14 (38.9)	<0.0001
Aspirin use, n (%)	0 (0.0)	25 (83.3)	8 (16.0)	33 (91.7)	<0.0001
Hydroxyurea use, n (%)	N/A	17 (56.7)	N/A	23 (63.9)	0.618
Disease duration, years	N/A	4.8 ± 3.2	N/A	5.1 ± 3.5	0.718

Values are expressed as mean ± standard deviation (SD) or n (%), as appropriate. p values represent global four-group comparisons, except hydroxyurea use and disease duration, which were compared between the PV and PV+MetS groups. N/A, not applicable. Renal function indicators (urea and creatinine) are presented in Table 1.

Significant differences were identified in platelet-related parameters (Table 1). Platelet counts were significantly higher in the PV group than in controls (363 ± 88.9 vs. 250.0 ± 61.2 × 10^3/μL, $p < 0.002$) and were highest in the PV+MetS group (378.2 ± 219.7 × 10^3/μL), which also differed significantly from the MetS group (279.9 ± 141.5 × 10^3/μL, $p < 0.02$) (Figure 1A). Similarly, PMI values differed significantly among groups ($p = 0.0007$), with higher values observed in the PV (3472 ± 1178, $p < 0.02$) and MetS groups (3381 ± 1466, $p < 0.05$) compared with controls. The highest PMI value was detected in the PV+MetS group (3646 ± 2143) (Figure 1B).

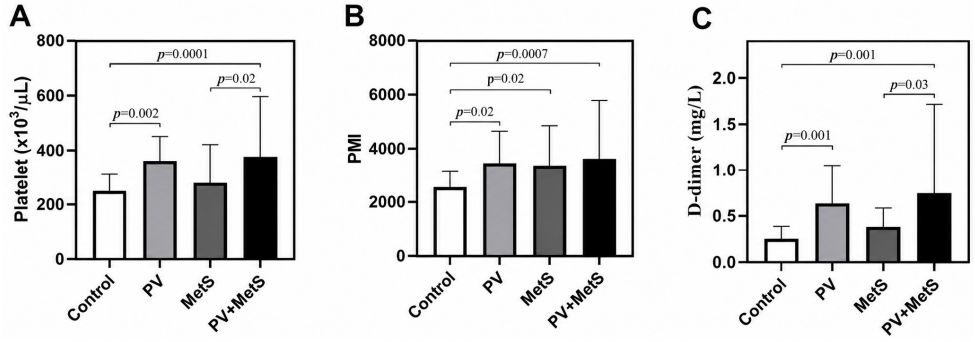


Figure 1. Comparison of platelet count (**A**), platelet mass index (PMI) (**B**), and D-dimer levels (**C**) among Control, Polycythemia Vera (PV), Metabolic Syndrome (MetS), and Polycythemia Vera with Concomitant Metabolic Syndrome (PV+MetS) groups. Data are presented as mean ± SD. Brackets indicate selected post hoc pairwise comparisons: platelet count, Control vs. PV $p < 0.002$ and MetS vs. PV+MetS $p < 0.02$; PMI, Control vs. PV $p < 0.02$ and Control vs. MetS $p < 0.05$; D-dimer, Control vs. PV $p < 0.001$ and MetS vs. PV+MetS $p < 0.03$.

Coagulation status, assessed by D-dimer levels, also varied significantly among groups ($p = 0.001$) (Table 1). Mean D-dimer concentrations were 0.25 ± 0.13 mg/L in controls, 0.38 ± 0.20 mg/L in MetS patients, 0.64 ± 0.41 mg/L in PV patients, and 0.75 ± 0.97 mg/L in PV+MetS patients. D-dimer levels were significantly elevated in the PV group compared with controls ($p < 0.001$) and in the PV+MetS group compared with the MetS group ($p < 0.03$) (Figure 1C).

Several biochemical parameters differed significantly among the groups (Table 1). Urea ($p = 0.0003$), creatinine ($p = 0.016$), total bilirubin ($p = 0.0001$), GGT ($p = 0.005$), magnesium ($p = 0.0075$), and LDH ($p < 0.0001$) levels showed significant intergroup variation. In addition, copper and zinc concentrations differed significantly among groups (both $p = 0.01$).

Oxidative stress markers demonstrated marked alterations across the study groups (Table 1, Figure 2). TAS levels were highest in controls (11.05 ± 2.86 mmol Trolox Eq/L) and lowest in the PV+MetS group (8.35 ± 2.00 mmol Trolox Eq/L). TAS values were significantly lower in the PV+MetS group than in controls ($p < 0.0001$) and the MetS group ($p = 0.007$) (Figure 2).

TOS values were 1.387 ± 0.28, 0.931 ± 0.35, 1.149 ± 0.42, and 1.457 ± 0.30 μmol H_2O_2 Eq/L in the control, PV, MetS, and PV+MetS groups, respectively. Compared with controls, PV patients exhibited significantly lower TOS levels ($p = 0.002$). TOS values were also lower in the PV group than in the MetS group ($p = 0.03$), whereas the PV+MetS group showed significantly higher TOS levels than the PV group ($p = 0.0003$). In addition, TOS values were significantly higher in the PV+MetS group than in controls ($p < 0.0001$) (Figure 2).

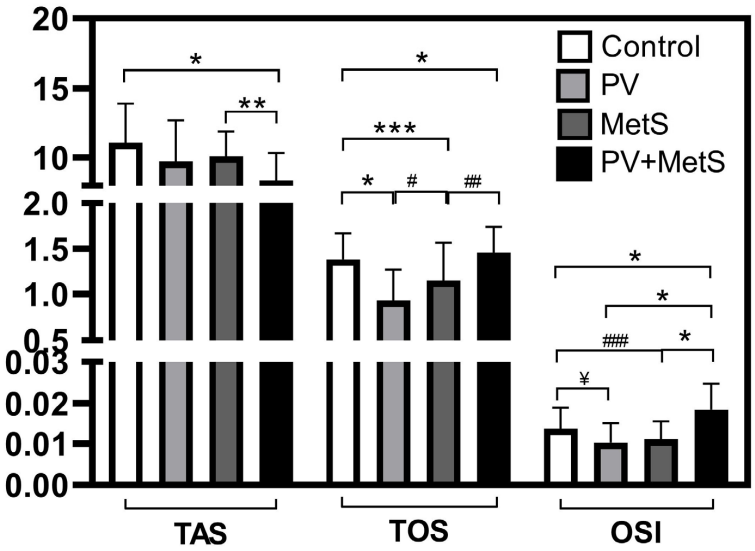


Figure 2. Comparison of oxidative stress parameters (TAS, TOS, and OSI) in Control, PV, MetS, and PV+MetS groups. Data are presented as mean ± SD. Brackets indicate selected post hoc pairwise comparisons. TAS: Control vs. PV+MetS $p < 0.0001$ and MetS vs. PV+MetS $p = 0.007$. TOS: Control vs. PV $p = 0.002$, PV vs. MetS $p = 0.03$, PV vs. PV+MetS $p = 0.0003$, and Control vs. PV+MetS $p < 0.0001$. OSI: Control vs. PV $p = 0.02$, Control vs. PV+MetS $p < 0.0001$, PV vs. PV+MetS $p = 0.048$, and MetS vs. PV+MetS $p < 0.0001$ (* $p < 0.0001$, ** $p = 0.007$, *** $p = 0.002$, # $p = 0.03$, ## $p = 0.0003$, ### $p = 0.01$, ¥ $p = 0.02$).

OSI values differed significantly among groups ($p < 0.0001$) (Table 1). The lowest OSI value was observed in the PV group (0.01026 ± 0.0047 AU), whereas the highest value was detected in the PV+MetS group (0.01851 ± 0.0062 AU). Compared with controls, OSI values were significantly lower in PV patients ($p = 0.02$). In contrast, the PV+MetS group exhibited significantly higher OSI values than the control ($p < 0.0001$), PV ($p = 0.048$), and MetS groups ($p < 0.0001$) (Figure 2).

D-dimer (AUROC = 0.799), LDH (0.763), total bilirubin (0.743), TAS (0.774), and OSI (0.750) showed the highest exploratory discriminatory performance ($p < 0.001$). D-dimer, LDH, and PMI demonstrated the highest specificity (Table 3 and Figure 3).

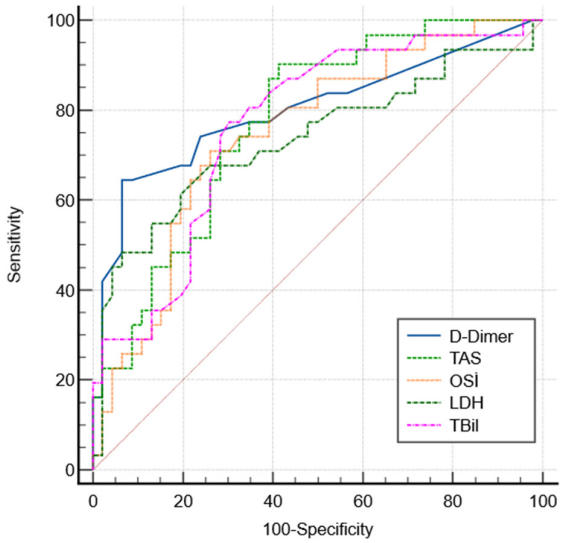


Figure 3. Exploratory discriminatory performance of TAS (AUC:0.774), OSI (AUC:0.750;), D-dimer (AUC:0.799), LDH (AUC:0.763), and total bilirubin (AUC:0.743): ROC curve analysis in patients with polycythemia vera and concomitant metabolic syndrome.

Table 3. Exploratory discriminatory performance of laboratory parameters for distinguishing patients with concomitant PV and MetS from the other study groups: ROC curve analysis.

Parameter	AUROC	95% CI	Cut-Off	Sensitivity (%)	Specificity (%)	*p* Value
Platelets	0.662	0.553–0.760	>303	50.00	90.57	0.0149
PMI	0.643	0.533–0.743	>3346.2	50.00	94.34	0.0438
Urea	0.701	0.594–0.793	>25.9	63.89	71.70	0.0004
Creatinine	0.673	0.565–0.768	>0.86	52.78	77.36	0.0044
Total bilirubin	0.743	0.639–0.830	>0.37	80.56	62.26	<0.0001
GGT	0.676	0.568–0.771	>27	55.56	79.25	0.0025
LDH	0.763	0.661–0.847	>203	52.78	94.34	<0.0001
Magnesium	0.663	0.555–0.760	≤2.17	83.33	45.28	0.0057
Copper	0.665	0.555–0.762	>126	65.71	75.00	0.0129
Zinc	0.673	0.565–0.768	>0.86	52.78	77.36	0.0044
D-dimer	0.799	0.692–0.882	>0.34	64.52	93.48	<0.0001
TAS	0.774	0.673–0.856	≤10.005	83.33	62.26	<0.0001
OSI	0.750	0.647–0.836	≤0.625	69.44	75.47	<0.0001

AUROC: Area under the receiver operating characteristic curve. CI: Confidence interval. PMI: Platelet Mass Index; GGT: Gamma-glutamyl transferase; LDH: Lactate dehydrogenase; TAS: Total antioxidant status; OSI: Oxidative stress index. A p value < 0.05 was considered statistically significant.

Pearson correlation analysis was performed to evaluate the relationships among hematological, biochemical, coagulation, and oxidative stress parameters (Figure 4).

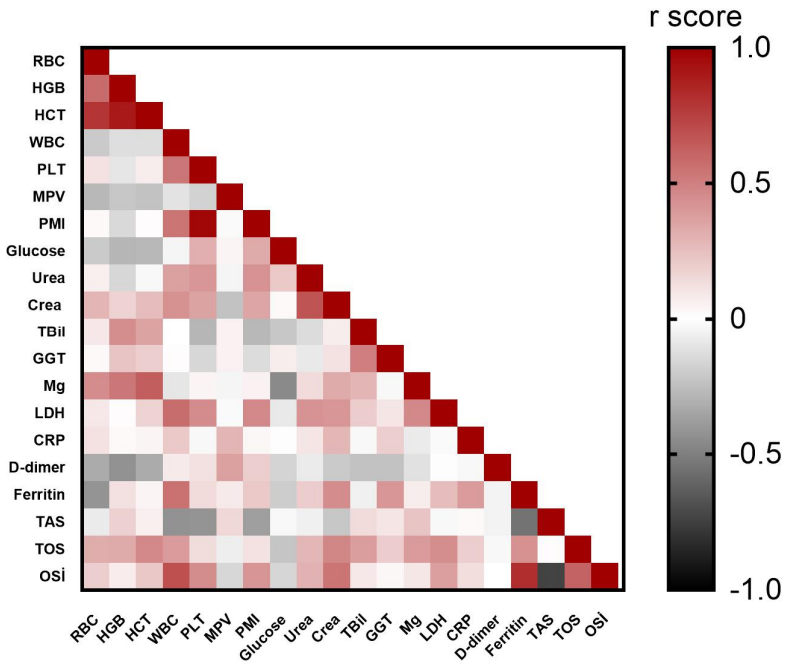


Figure 4. Pearson correlation analysis of hematological, biochemical, coagulation, and oxidative stress markers in patients with PV and concomitant MetS. Color intensity represents Pearson correlation coefficients (r); red indicates positive correlations and gray/black indicates negative correlations. The principal numerical r values are reported in the Results section.

Strong positive correlations were observed among erythrocyte-related parameters. Hemoglobin showed a very strong correlation with hematocrit (r = 0.90), while red blood cell count was strongly correlated with hematocrit (r = 0.79) and moderately correlated with hemoglobin (r = 0.58). White blood cell count demonstrated moderate positive correlations with platelet count (r = 0.53), platelet mass index (PMI) (r = 0.54), lactate dehydrogenase (LDH) (r = 0.57), ferritin (r = 0.55), and oxidative stress index (OSI) (r = 0.68).

As expected, platelet count exhibited a very strong positive correlation with PMI ($r = 0.97$). In addition, platelet count showed moderate positive correlations with LDH ($r = 0.45$) and OSI ($r = 0.45$), whereas a moderate negative correlation was observed with TAS ($r = -0.42$). PMI was positively correlated with glucose ($r = 0.33$), urea ($r = 0.42$), creatinine ($r = 0.35$), ferritin ($r = 0.21$), and OSI ($r = 0.41$), while demonstrating a negative correlation with TAS ($r = -0.38$).

Among biochemical markers, urea showed a strong positive correlation with creatinine ($r = 0.67$). Total bilirubin was moderately correlated with GGT ($r = 0.50$). LDH demonstrated moderate positive correlations with WBC ($r = 0.57$), platelet count ($r = 0.45$), PMI ($r = 0.46$), magnesium ($r = 0.46$), urea ($r = 0.42$), creatinine ($r = 0.41$), TOS ($r = 0.44$), and OSI ($r = 0.37$).

Ferritin exhibited moderate positive correlations with WBC ($r = 0.55$), creatinine ($r = 0.45$), GGT ($r = 0.41$), CRP ($r = 0.39$), and TOS ($r = 0.43$). Notably, ferritin demonstrated the strongest positive correlation with OSI ($r = 0.82$) and a moderate negative correlation with TAS ($r = -0.55$).

Oxidative stress parameters showed significant interrelationships. TOS was positively correlated with hematocrit ($r = 0.46$), creatinine ($r = 0.47$), ferritin ($r = 0.43$), LDH ($r = 0.44$), and WBC count ($r = 0.39$). TAS demonstrated moderate negative correlations with WBC ($r = -0.43$), platelet count ($r = -0.42$), PMI ($r = -0.38$), and ferritin ($r = -0.55$). OSI showed strong positive correlations with ferritin ($r = 0.82$), WBC count ($r = 0.68$), and TOS ($r = 0.61$), while exhibiting a strong inverse correlation with TAS ($r = -0.74$). Moderate positive correlations were also observed between OSI and creatinine ($r = 0.54$), platelet count ($r = 0.45$), PMI ($r = 0.41$), and LDH ($r = 0.37$).

D-dimer demonstrated generally weak associations with other laboratory parameters. The strongest correlations were negative correlations with hemoglobin ($r = -0.43$), RBC count ($r = -0.33$), and hematocrit ($r = -0.33$), whereas only weak positive correlations were observed with platelet-related parameters.

Overall, the correlation analysis revealed a close association among platelet burden, cellular turnover, inflammatory activity, and oxidative stress markers. The strong positive correlation between ferritin and OSI and the strong inverse correlation between TAS and OSI suggest that oxidative stress is closely linked to inflammatory activity and disease-related biological burden in patients with PV and concomitant metabolic syndrome.

4. Discussion

In this cross-sectional comparative study, hematological, biochemical, coagulation, trace-element, and oxidative stress parameters were evaluated among patients with polycythemia vera (PV), metabolic syndrome (MetS), concomitant PV and MetS (PV+MetS), and healthy controls. The main findings were that patients with PV+MetS exhibited higher platelet count, platelet mass index (PMI), D-dimer, total oxidant status (TOS), and oxidative stress index (OSI) values, together with lower total antioxidant status (TAS) levels compared with the other study groups. These findings suggest that the coexistence of PV and MetS is associated with a distinct laboratory phenotype involving platelet-related, coagulation-related, and oxidative stress pathways. However, because of the cross-sectional design, these findings should be interpreted as exploratory laboratory associations rather than evidence of clinical risk prediction or validated risk stratification.

PV is a chronic myeloproliferative neoplasm characterized by clonal hematopoiesis, increased red cell mass, variable leukocytosis and thrombocytosis, and a well-recognized predisposition to arterial and venous thrombosis. Although erythrocytosis and hyperviscosity are central features of PV, thrombotic complications are influenced by multiple biological processes, including platelet activation, leukocyte–platelet interactions, endothe-

lial dysfunction, inflammation, and activation of coagulation pathways [16,17]. Current reviews also emphasize that conventional PV assessment should consider age, thrombosis history, hematocrit control, vascular risk factors, and disease-related biological activity [1]. In the present study, platelet counts were significantly higher in PV patients than in controls and reached the highest levels in the PV+MetS group. This finding is consistent with the proliferative biology of PV and suggests that concomitant metabolic abnormalities may be associated with additional platelet-related laboratory alterations.

PMI was also significantly elevated in the patient groups, particularly in patients with concomitant PV and MetS. PMI integrates platelet count and mean platelet volume and may therefore reflect total circulating platelet burden more comprehensively than platelet count alone. Although MPV alone showed limited discriminatory value, the increase in PMI suggests that combined evaluation of platelet number and platelet size may provide additional information regarding platelet-related laboratory changes. Platelet abnormalities in myeloproliferative neoplasms are not limited to platelet quantity; platelet heterogeneity, functional alterations, and disease-specific platelet phenotypes may also contribute to inflammatory and thrombotic biology [18]. Nevertheless, in the absence of thrombotic outcome data and prospective follow-up, PMI should be regarded as an exploratory marker of platelet-related burden rather than a clinically validated risk marker.

MetS is characterized by insulin resistance, central obesity, dyslipidemia, hypertension, and chronic low-grade inflammation. These metabolic disturbances are closely related to endothelial dysfunction, oxidative stress, platelet activation, and impaired fibrinolysis. Therefore, in patients with PV, the coexistence of MetS may create a biological environment in which clonal myeloproliferation and metabolic inflammation converge. The higher platelet count observed in the PV+MetS group compared with the MetS group supports the possibility that the combined condition is associated with a more pronounced platelet-related laboratory phenotype. However, this observation should not be interpreted as evidence that PV+MetS independently increases thrombotic risk, since thrombotic events, treatment effects, and prospective clinical outcomes were not evaluated in this study.

D-dimer levels were significantly increased in the PV and PV+MetS groups, with the highest values observed in patients with concomitant disease. D-dimer is a marker of fibrin formation and degradation and reflects activation of coagulation and fibrinolysis. Elevated D-dimer levels may indicate subclinical coagulation activation, although this marker is nonspecific and may be influenced by inflammation, age, comorbidities, and other clinical factors [19]. In the present study, D-dimer levels were significantly higher in PV patients than in controls and in PV+MetS patients than in MetS patients. These findings suggest that PV-related coagulation activation may coexist with metabolic and inflammatory alterations in patients with concomitant disease. However, because clinically confirmed thrombotic outcomes were not included, D-dimer should be interpreted only as an exploratory laboratory indicator of coagulation activation in this cohort.

The biochemical findings also suggest broader systemic laboratory alterations in PV+MetS. Urea, creatinine, total bilirubin, GGT, LDH, copper, and zinc levels differed significantly among the groups. LDH showed moderate discriminatory performance in ROC analysis and may reflect increased cellular turnover, tissue stress, and myeloproliferative activity [20]. Elevated bilirubin and GGT may be related to hepatic metabolic stress, oxidative burden, or altered redox homeostasis. MetS is closely associated with hepatic steatosis, insulin resistance, and metabolic liver injury, whereas PV may contribute to increased cellular turnover and systemic inflammation [5,21]. Therefore, the biochemical profile observed in PV+MetS may reflect the combined laboratory effects of hematologic proliferation and metabolic dysfunction. Nevertheless, these biochemical parameters are

nonspecific and cannot be considered disease-specific or prognostic markers based on the present study design.

An additional noteworthy finding was the marked elevation of zinc concentrations in the PV+MetS group. Although this observation may initially appear unexpected, disturbances in trace-element homeostasis have been described in chronic inflammatory and oxidative stress-related conditions. Zinc is involved in antioxidant defense, immune regulation, DNA synthesis, and cellular proliferation. Therefore, increased zinc concentrations may reflect adaptive or compensatory responses to persistent inflammation, oxidative stress, or increased cellular turnover. A recent systematic review and meta-analysis also supports the relationship between zinc status, inflammation, and oxidative stress biomarkers in adults [22]. However, the literature regarding zinc status in patients with concomitant PV and MetS remains limited and inconsistent. This finding should therefore be interpreted cautiously and requires confirmation in larger and better-controlled prospective studies.

Oxidative stress represents an important biological link between PV, MetS, inflammation, endothelial dysfunction, and coagulation activation. In this study, TAS was significantly reduced in the PV+MetS group, whereas OSI was significantly increased. TAS reflects overall antioxidant defense capacity, while OSI represents the balance between oxidant burden and antioxidant reserve. The finding that TAS was lowest and OSI was highest in PV+MetS suggests that patients with concomitant disease may have a more pronounced redox imbalance. This is biologically plausible because oxidative stress may contribute to endothelial damage, platelet activation, lipid peroxidation, inflammatory signaling, and thrombus formation [7,12]. However, the present data demonstrate laboratory associations only and do not establish whether oxidative stress contributes directly to thrombotic or cardiovascular outcomes in this patient population.

Interestingly, TOS values were lowest in the PV group and highest in the PV+MetS group. At first glance, the lower TOS levels observed in PV patients compared with healthy controls may appear counterintuitive. One possible explanation is the effect of disease-related treatment, including hydroxyurea, phlebotomy, and low-dose aspirin, which may attenuate oxidative and inflammatory activity. Another possible explanation is heterogeneity in disease activity, disease duration, treatment response, and comorbid conditions among PV patients. In addition, TOS alone may not fully reflect oxidative imbalance, particularly when antioxidant capacity varies substantially between groups. OSI may provide a more integrated assessment because it incorporates both oxidant status and antioxidant defense. Therefore, the elevated OSI in PV+MetS, despite variable TOS patterns, may indicate that oxidative imbalance in these patients is related not only to oxidant production but also to reduced antioxidant capacity. Since treatment-specific subgroup analyses and comprehensive JAK2 allele burden data were not available for all patients, the mechanisms underlying this finding remain uncertain. Future studies incorporating treatment status, disease activity measures, metabolic parameters, and JAK2 mutational burden are needed to clarify this observation.

The coexistence of PV and MetS may be associated with redox imbalance through multiple converging mechanisms. In PV, JAK2-driven clonal hematopoiesis, increased cell turnover, leukocyte activation, and inflammatory cytokine release may contribute to reactive oxygen species generation and endothelial injury. In MetS, insulin resistance, adipose tissue inflammation, mitochondrial dysfunction, hyperglycemia, and dyslipidemia may increase oxidative stress and reduce antioxidant defense. When these two conditions coexist, these mechanisms may overlap and produce a laboratory pattern characterized by higher OSI and lower TAS. The increased OSI and reduced TAS observed in the PV+MetS group are consistent with overlapping pathway involvement; however, formal interaction/additivity

analyses were not performed, and causality cannot be inferred from the present cross-sectional data.

ROC analysis showed that D-dimer, TAS, OSI, LDH, and total bilirubin had moderate discriminatory performance for distinguishing patients with PV+MetS from controls. Among these parameters, D-dimer had the highest AUC, suggesting that coagulation activation was one of the most prominent laboratory differences observed in the comorbid group. TAS and OSI also showed moderate discriminatory ability, indicating that oxidative stress parameters may complement conventional hematological and biochemical markers in characterizing the PV+MetS laboratory phenotype. Importantly, these ROC findings should not be interpreted as evidence of diagnostic, prognostic, or risk-stratification utility. The analysis was exploratory, was not externally validated, and was not linked to thrombotic or cardiovascular outcomes. Therefore, these biomarkers should be considered hypothesis-generating laboratory markers rather than tools for clinical decision-making.

The correlation analysis provides additional support for the interconnected nature of hematological, biochemical, coagulation, and oxidative stress pathways in PV+MetS. Although correlation analysis cannot establish causality, the observed relationships suggest that platelet-related indices, D-dimer, LDH, ferritin, TAS, TOS, and OSI may be part of a shared biological network involving myeloproliferation, inflammation, coagulation activation, and redox imbalance. These findings support the concept that concomitant PV and MetS may be associated with overlapping laboratory alterations across multiple biological systems. However, these correlations should be interpreted cautiously because they do not demonstrate directionality, independence, or prognostic relevance.

From a clinical perspective, the present findings should be interpreted with appropriate caution. Although platelet indices, D-dimer, LDH, TAS, and OSI differed among the study groups, the absence of thrombotic outcome data, prospective follow-up, treatment-adjusted models, and external validation prevents these markers from being used for clinical risk stratification. Instead, these parameters may help characterize the exploratory laboratory phenotype of patients with concomitant PV and MetS. Their potential prognostic value should be tested in larger prospective cohorts that include thrombotic and cardiovascular outcomes, standardized treatment data, metabolic risk variables, and validation analyses.

Several limitations should be considered. First, the cross-sectional design prevents causal inference. Therefore, it cannot be determined whether oxidative stress and coagulation activation are causes or consequences of the comorbid state. Second, the study was conducted at a single center and included a relatively limited number of participants, which may restrict generalizability. Third, treatment-related variables, including phlebotomy, cytoreductive therapy, antiplatelet therapy, and metabolic medications, as well as cardiometabolic factors such as BMI, diabetes, hypertension, statin use, antihypertensive use, antidiabetic medication, and smoking, may influence platelet count, D-dimer, LDH, ferritin, renal function, and oxidative stress parameters. These variables were summarized descriptively, but treatment-adjusted multivariable models and sensitivity analyses were not performed because of treatment heterogeneity, limited subgroup sizes, and the absence of thrombotic outcome data. Fourth, JAK2 mutational status and allele burden were not available for all patients and therefore could not be incorporated into the analysis. In addition, subgroup analyses according to disease duration, thrombotic history, body mass index, diabetes status, medication use, and individual MetS components were not performed. Future studies should address these factors to clarify the independent and combined effects of PV and MetS on thromboinflammatory and oxidative stress pathways.

Despite these limitations, the present study has several strengths. The inclusion of separate PV, MetS, PV+MetS, and control groups allowed for the direct comparison of isolated and concomitant disease states. In addition, the simultaneous evaluation of hema-

tological, biochemical, coagulation, trace-element, and oxidative stress parameters provided a broad laboratory assessment of the biological alterations associated with PV+MetS. The integration of group comparisons, ROC analysis, and correlation analysis further supports the exploratory interpretation of the findings.

Overall, the present results indicate that concomitant PV and MetS are associated with increased platelet burden, higher D-dimer levels, impaired antioxidant defense, and elevated oxidative stress markers. These alterations suggest a distinct thromboinflammatory and redox-related laboratory phenotype in patients with PV and metabolic comorbidity. However, these findings should be considered exploratory and hypothesis-generating. They do not establish causality, prognostic value, or clinical risk-stratification utility.

5. Conclusions

In conclusion, concomitant PV and MetS were associated with higher platelet burden, increased D-dimer levels, reduced antioxidant capacity, and elevated oxidative stress markers compared with the other study groups. These findings suggest that PV+MetS may be characterized by a distinct laboratory profile involving platelet-related, coagulation-related, and oxidative stress pathways. However, given the cross-sectional, single-center design and the lack of thrombotic outcome data, prospective follow-up, treatment-adjusted analyses, and validation cohorts, these markers should be interpreted as exploratory laboratory associations rather than tools for clinical risk stratification. Larger prospective studies including thrombotic and cardiovascular outcomes, treatment-adjusted models, and validation cohorts are needed to determine whether these parameters have prognostic value in patients with PV and metabolic comorbidity.

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