Sohag University | Sohag Medical Journal | Faculty of Medicine

Original Article

Carotid Plaque Burden and Neutrophil-Lymphocyte Ratio in Patients with Philadelphia Negative Myeloproliferative Neoplasms and Their Relation to JAK2 V617F Mutation

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Abstract

Background: Philadelphia negative myeloproliferative neoplasms (PN-MPNs), is characterized by clonal myeloid cell proliferation. The JAK2V617F mutation, prevalent in PN-MPNs, may influence inflammation and atherosclerosis. Neutrophil-Lymphocyte Ratio (NLR) and carotid plaque burden are markers associated with inflammation and cardiovascular risk, respectively.

Aim: This study aimed to investigate the relationship between NLR, carotid plaque burden, and JAK2V617F mutation in PN-MPN patients.

Patients and Methods: A retrospective case-control study included 90 PN-MPN patients and 60 controls. Data on demographics, comorbidities, thrombosis, laboratory parameters, carotid plaque burden, and JAK2V617F mutation status were collected.

Results: The study included 90 PN-MPNs patients and 60 healthy controls. Age, gender distribution, smoking status, and comorbidities did not significantly differ between PN-MPN patients and controls. Thrombosis incidence in PN-MPN patients did not significantly differ from controls. Carotid plaque burden and NLR were significantly higher in PN-MPN patients compared to controls ($p=0.024$ and $p<0.001$, respectively). Majority of PN-MPN patients (78.9%) had positive JAK2V617F mutation status. NLR was significantly higher in PN-MPN patients with positive JAK2V617F mutation compared to negative ($p=0.001$). There was no significant correlation between the IMT or plaque score and MPN patients with a positive JAK2V617F mutation. There was a significant difference in thrombosis incidence between patients with positive and negative JAK2V617F mutation status.

Conclusion: The study identified a significant link between higher N/L ratios and the JAK2V617F mutation in patients with PN-MPNs, proposing the N/L ratio as a potential marker for disease activity or mutation status. Despite observing a higher incidence of thrombosis in MPN patients and increased carotid plaque in PN-MPN patients compared to controls, no significant correlation was found between these cardiovascular risk markers and the JAK2V617F mutation status, suggesting other factors influence thrombosis risk in these patients.

Keywords: Philadelphia negative myeloproliferative neoplasms, JAK2V617F mutation, neutrophil-lymphocyte ratio, carotid plaque burden, inflammation, cardiovascular risk.

DOI : 10.21608/SMJ.2024.277625.1459

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Received: 17 March 2024
Revised: 22 March2024
Accepted: 03 April 2024
Published: 01 May 2024

Introduction

Philadelphia negative myeloproliferative neo-plasms (PN-MPNs), such as essential throm-bocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF), are types of blood cancers resulting from the abnormal growth of myeloid cells. PV is the most frequently diagnosed, followed by ET and PMF .(1) The outlook for individuals with MPNs can be affected by various factors, including the JAK2V617F mutation, other genetic changes like CALR and MPL mutations, the occurrence of blood clots, additional cancers, and the individual's age and gender. (2)

The development of PN-MPNs involves the abn-ormal growth of stem cells in the bone marrow, leading to too many blood cells. The most com-mon genetic change in these conditions is the JAK2V617F mutation, found in the majority of patients with PV, and in about half of those with ET or PMF. Research indicates that this genetic change is linked to higher levels of NETs, which play a role in the development of blood clots in MPNs. Additionally, this mutation increases the risk of SVT in MPN patients. (3,4)

The Neutrophil-Lymphocyte Ratio (NLR) is an established marker of systemic inflammation, serving as a prognostic indicator in various conditions, including cardiovascular diseases. (5) Elevated NLR values are linked to poor outc-omes, reflecting an imbalance between inflammation and immune response .(6)

Carotid plaque burden, quantified through ima-ging techniques, is an independent predictor of cardiovascular events, such as stroke and myoc-ardial infarction .(7) This marker is crucial for assessing atherosclerotic disease risk. (8)

The JAK2V617F mutation, common in PV and ET, activates the JAK-STAT signaling pathway, playing a significant role in the development of these conditions .(9) It is also associated with increased inflammatory markers and may play a role in atherosclerosis .(10)

Research suggests a potential link between NLR, carotid plaque burden, and the JAK2V617F mutation in PN-MPN patients, which could explain the increased cardiovascular risk in these patients. (11)

The direct relationship between NLR, carotid plaque burden, and the JAK2V617F mutation in PN-MPN patients remains underexplored, repr-esenting a significant gap in the literature. Ther-efore, our study rational was investigation the relationship between NLR, carotid plaque bu-rden, and the JAK2V617F mutation in patients with PN-MPNs.

Patients and methods

Type of Study

This retrospective case-control study comparing patients with PN-MPNs diagnosed at Sohag Uni-versity Hospital between December 2022 and May 2023. The study followed WHO 2016 guidelines for diagnosis .(12)and was approved by the ethics committee of the Sohag Faculty of Medicine. We ensured patient awareness and confidentiality of data.

Inclusion Criteria

Patients 18 and older diagnosed with PN-MPNs at our hospital from November 2014 to October 2022 were included in the study.

Exclusion Criteria

Patients with other blood conditions like reactive thrombocytosis or polycythemia, or those prev-iously diagnosed with chronic or acute myeloid leukemia were excluded.

Data Collection

We retrospectively collected data on clinical ma-nifestations at diagnosis, history of thrombosis or hemorrhage.

All individuals undergone a comprehensive asse-ssment encompassing medical history, clinical examination, and investigations. Investigations included complete blood count (CBC) that was done by Abbott Cell-Dyn Ruby haematology analyser (Abbott Laboratories, Abbott Park, Illinois, USA). In addition, C-reactive protein estimation was carried out using the comer-cially available Kit (Agappe Diagnostics Ltd. India) with the automated chemical analyzer AGAPPE MISPA-i2 instrument based on nephelometry method. Serum creatinine,

uric acid and lipogram were done by an AU480 chemical analyzer (Beckman Coulter, Tokyo, Japan) and Cobas c311 Chemistry Analyser System (Roche Diagnostic GmbH, Indianopolis, IN, USA). JAK2V617F mutation status by real time PCR using QIAcube system (Qiagen, Hilden, Germany) with Spin tubes protocols (Qiagen) and The StepOne™ Real-Time PCR System (Applied Biosystems, Life Technologies, Foster City, CA, USA). Carotid plaque burden had been evaluated using Color Doppler ultrasonography.

The control group, matched for age, sex, and classical atherosclerosis risk factors (arterial hypertension, hyperlipidemia, diabetes, smoking, or obesity), consisted of apparently healthy volunteers.

The neutrophil-to-lymphocyte ratio was calcu-lated based on absolute peripheral granulocyte (as a proxy for neutrophil count) (N; 10^9/L) and lymphocyte (L; 10^9/L) blood counts, using the following formula: NLR = N/L.

Carotid ultrasonography

We position the patient flat on their back, neck stretched and head turned opposite the examination side, allowing clear access to the carotid arteries. Using the LOGIQ® F6 (General Electric, USA) ultrasound machine with a high-definition L6-12-MHz probe, we examine the carotid arteries for atheromatous plaques, noting their presence, size, and makeup by scanning in two directions. Scoring of plaques is from 0 (no plaques) to 6 (plaques in every sector). [13], based on their impact on the artery's opening and their visual and surface characteristics. Following this, we use Color Doppler to study blood movement near and through these plaques to identify narrowing and irregular flow indicating progression of artery-hardening disease. We measure the severity of narrowing to classify plaque risk, using Doppler spectral analysis. This detailed Doppler study helps in risk assessment for heart-related issues, aiding in decision-making for patient care.

Statistical analysis

We gathered and coded the information, then input it into a Microsoft Excel 2016 spreadsheet. Afterward, we analyzed the data using IBM's SPSS software, 21st edition. To check if our continuous data followed a normal distribution, we applied the Kolmogorov-Smirnov Test. We reported our findings using counts and perc-entages for category-based data, and averages, standard deviations, and ranges for number-based data that fits a normal pattern. For data that didn't fit this pattern, we used medians and interquartile ranges. To test our hypotheses, we utilized Chi-square, Mann Whitney, Kruskal-Wallis, and Monte-Carlo correction tests, cons-idering results with a P value less than 0.05 as significant.

Results

The study included a total of 90 patients with PN-MPNs and 60 healthy individuals as con-trols.

Table (1): Comparison between subtypes of MPN and controls regarding demographic characteristics.

		PV patients (n=36)		ET patients (n=26)		MF patients (n=28)		Total MPN patients (n=90)		Controls (n=60)		*P*- value[a]	*P*- value[b]
		N	%	N	%	N	%	N	%	N	%		
Gender	**Male**	24	66.7%	9	34.6%	8	28.6%	41	45.6%	28	46.7%	0.326[∓]	p1=0.092, p2=0.424, p3=0.169
	Female	12	33.3%	17	65.4%	20	71.4%	49	54.4%	32	53.3%		
Age (years)	**Mean± SD Range**	54.69± 13.79 30- 75		57.19± 12.07 31- 74		62.04± 12.97 31- 82		57.7± 13.28 30- 82		61.42± 2.95 54- 68		0.894[‡]	p1=0.562, p2=0.842, p3=0.135
Smoking	**Smoker**	12	33.3%	1	3.8%	2	7.1%	15	16.7%	15	25.0%	0.454[‡]	**p1=0.006,** p2=0.044, p3=0.087
	Non-smoker	17	47.2%	23	88.5%	24	85.7%	64	71.1%	38	63.3%		
	X-smoker	7	19.4%	2	7.7%	2	7.1%	11	12.2%	7	11.7%		
Comorbidities	**DM**	6	16.7%	4	15.4%	4	14.3%	14	15.6%	5	8.3%	0.193[‡]	0.619[‡]
	HTN	13	36.1%	11	42.3%	14	50.0%	38	42.2%	14	23.3%		0.071[‡]
	Dyslipidemia	4	11.1%	6	23.1%	4	14.3%	14	15.6%	6	10.0%		0.409[‡]
Thrombosis	**No**	22	61.1%	20	76.9%	14	50.0%	56	62.2%	-		0.103[MC‡]	P4=0.328 P5=0.092 P6=0.117
	Yes	14	38.9%	6	23.1%	14	50.0%	34	37.8%				
Type of thrombosis	**Arterial**	6	16.7%	2	7.7%	5	17.9%	13	14.4%	-		0.261[MC‡]	P4=0.507 P5=0.377 P6=0.155
	Venous	8	22.2%	4	15.4%	9	32.1%	21	23.3%				
Duration (months)	**Mean± SD**	23.19± 24.5		24.08±14.77		16.25±17.78		21.29±20.12		-		**0.041[¥]**	P4=0.099 P5=0.308 **P6=0.012**

presents a comparison between the subtypes of MPN (PV, ET, and MF) and controls regarding demographic characteristics. The mean age of PV patients was 54.69 ±13.79 years, while the mean age of ET patients was 57.19 ±12.07 years and the mean age of MF patients was 62.04 ±12.97 years. The mean age of the total MPN patient group was 57.7 ±13.28 years. Gender distribution among MPN patients was 45.6% male. Age, gender distribution and smoking status did not differ significantly between MPN patients and controls. Prevalence of comorbidities (DM, HTN, Dyslipidemia) varied among MPN subtypes, but none were significantly different from controls. Thrombosis incidence in MPN patients (37.8%) without signfifcant difference among different types of MPN (p> 0.05). Among MPN patients with thrombosis, venous thrombosis was the most common type (23.3%).

Table (2): Comparison between subtypes of MPN and controls regarding routine laboratory Data

	PV patients (n=36)			ET patients (n=26)			MF patients (n=28)			Total MPN patients (n=90)			Controls (n=60)		*P*- value[a]		*P*- value[b]
	Median	IQR		Median	IQR		Median	IQR		Median	IQR		Median	IQR			
WBCs	10.10	8.20	13.25	11.95	7.70	20.0	14.70	9.60	21.0	10.50	8.20	18.0	5.66	4.77	6.28	**<0.001**	**p1<0.001, p2<0.001, p3<0.001**
N/L ratio	2.33	1.62	3.62	3.40	2.62	4.07	3.11	2.42	3.97	2.97	2.11	3.87	1.87	0.80	2.94	**<0.001**	**p1=0.010, p2<0.001, p3<0.001**
HB	19.0	18.0	19.65	12.10	11.5	14.0	9.5	8.45	15.4	15.35	11.3	19.0	12.95	12.26	13.64	**0.005**	**p1<0.001**, **p2=1.00, p3=1.00**
PLT	311.0	246.5	534.0	1035.0	909.0	1277.0	640.0	166.0	1342.0	641.0	276.0	1029.0	231.5	204.0	253.0	**<0.001**	**p1=0.006, p2<0.001, p3=0.005**
ESR	10.0	5.0	14.0	12.0	9.0	15.0	16.0	9.5	62.5	12.0	6.0	16.0	24.00	23.0	26.0	**<0.001**	**p1<0.001,** p2**<0.001,** p3=0.507
CRP (mg/L)	6.0	6.0	8.0	11.5	6.0	24.0	16.5	9.0	31.5	8.0	6.0	24.0	3.05	2.25	4.15	**<0.001**	**p1<0.001, p2<0.001, p3<0.001**
Uric acid (mg/dL)	6.35	5.30	7.15	5.60	3.6	6.6	7.1	5.6	8.65	6.25	5.4	7.30	23.78	23.03	24.24	**<0.001**	**p1<0.001, p2<0.001, p3<0.001**
GFR	95.6	78.0	111.0	89.5	79.0	95.0	55.0	42.0	95.5	91.0	65.0	100.0	45.0	37.4	52.30	**<0.001**	**p1<0.001,** p2**<0.001,** p3**=0.016**
LDH	305.0	247.5	355.5	310.0	241.0	420.0	516.0	435.0	625.0	345.0	250.0	512.0	214.0	176.0	250.5	**<0.001**	**p1<0.001, p2<0.001, p3<0.001**
Cholesterol (mg/dL)	169.0	146.0	188.0	170.0	146.0	190.0	165.0	150.0	180.0	170.0	148.0	190.0	177.0	166.5	189.0	**0.025**	0.095
LDL (mg/dL)	95.0	84.0	122.0	107.5	85.0	120.0	98.0	87.5	110.0	97.0	85.0	110.0	123.0	109.0	136.0	**<0.001**	**p1<0.001, p2=0.006, p3<0.001**
HDL (mg/dL)	42.0	40.0	45.0	41.5	40.0	45.0	40.0	38.5	43.0	41.0	40.0	45.0	57.50	42.5	72.50	**<0.001**	**p1<0.001, p2=0.005, p3<0.001**
TG (mg/dL)	130.0	105.0	180.0	130.0	100.0	160.0	130.0	103.0	160.0	130.0	105.0	160.0	126.5	109.0	140.0	0.192	0.631
Hematocrit	56.0	53.0	58.0	56.0	53.0	57.0	53.0	52.5	57.0	54.0	53.0	58.0	43.50	41.65	45.35	**<0.001**	**p1<0.001,** p2=1.00**, p3<0.001**
RDW	14.5	13.0	18.3	13.0	12.1	14.5	12.5	11.8	16.8	13.0	12.10	16.8	17.45	15.95	18.95	**<0.001**	**p1=0.002,** p2**<0.001,** p3**<0.001**

presents a comparison between the subtypes of MPN and controls regarding routine laboratory data. There were significant differences in white blood cell count (WBC), neutrophil-to-lymphocyte ratio (N/L ratio), hemoglobin (HB), platelet count (PLT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), uric acid, glomerular filtration rate (GFR), lactate dehydrogenase (LDH), cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TG), hematocrit, and red cell distribution width (RDW) between the MPN patients and controls ($p<0.001$ for all parameters except HB, cholesterol, and TG). N/L ratio was significantly higher in ET patients (3.40) followed by MF patients (3.11) and PV patients (2.33) than control (1.87)

Regarding the comparison between the subtypes of MPN and controls regarding splenic size, intima-media thickness (IMT), plaque score, and JAK2V617F mutation status. The IMT and plaque scores were significantly higher in the MPN patients compared to controls ($p=0.024$ for IMT and $p=0.011$ for plaque score). The majority of MPN patients (78.9%) had a positive JAK2V617F mutation status

Table (3): Comparison between subtypes of MPN and controls regarding IMT, plaque score and JAK mutation.

		PV patients (n=36)		ET patients (n=26)		MF patients (n=28)		Total MPN patients (n=90)		Controls (n=60)	*P*-value[a]	*P*- value[b]
IM thickness (mm)	**Median (IQR)**	0.82 (0.7-1.1)		0.8 (0.7-0.93)		0.8 (0.63-0.9)		0.8 (0.7- 1.0)		0.69 (0.55-0.88)	**0.024**‡	**p1=0.017,** p2=0.461, p3=0.485
Plaque score	**Median (IQR)**	1.88 (1.17-2.47)		1.75 (1.32-2.29)		2.0 (1.0- 2.8)		1.81 (1.0-2.42)		1.0 (1.0- 2.0)	**0.011**‡	**p1=0.028,** p2=0.168, **p3=0.040**
JAK2V617F mutation status	**Positive**	32	88.9%	18	69.2%	21	75.0%	71	78.9%	-	-	0.517‡
	Negative	4	11.1%	8	30.8%	7	25.0%	19	21.1%			

According to the correlation between the N/L ratio and different parameters in MPN patients with positive and negative JAK2V617F mutation status. The N/L ratio was significantly higher in MPN pati-ents with a positive JAK2V617F mutation com-pared to those with a negative mutation ($p=0.001$). There was no significant correlation between the IMT or plaque score and MPN patients with a positive JAK2V617F mutation

Table (4): Correlation between N/L ratio and different parameters.

	JAK2V617F mutation													p- value
	Positive							Negative						
	Mean	±SD	Median	IQR		Range		Mean	±SD	Median	IQR		Range	
N/L ratio	4.21	±3.89	3.48	2.32	-4.79	1.03	-23.06	2.38	±0.75	2.19	1.86	-3.0	0.96 - 3.87	**0.001**
IM thickness	0.82	±0.19	0.80	0.70	-0.9	0.60	-1.40	0.83	±0.24	0.75	0.60	-1.1	0.60 -1.3	0.469
plaque score	1.27	±0.65	1.00	1.00	-1.0	1.00	-4.00	1.78	±1.45	1.00	1.00	-2.0	1.00 -6.0	0.077

Table (5): Correlation between JAK2V617F mutation and thrombosis in MPN patients.

		JAK2V617F mutation				p- value‡
		Positive (n=71)		Negative (n=19)		
		N	%	N	%	
Thrombosis	**No**	43	60.6%	13	68.4%	**0.027**
	Yes	30	40.8%	4	26.3%	
Type of thrombosis	**Arterial**	11	15.5%	2	10.5%	0.584
	Venous	18	25.4%	3	15.8%	0.383

displays the relation between JAK2V617F mutation and thrombosis in MPN patients. In patients with thrombosis, 43.7% had the mutation (n=31), while 15.8% did not (n=3) with significant difference (p value of 0.027). The analysis further divides thrombosis into arterial (p-value of 0.584) and venous (p-value of 0.383), suggesting a nonsignificant correlation between the JAK2V617F mutation and arterial and venous thrombosis.

Discussion

Philadelphia negative MPNs, a group of blood cell production disorders in the bone marrow, often feature the JAK2V617F mutation, linked to increased inflammation and clotting risks .[14]

The connections between neutrophil-to-lymphocyte ratio (NLR), artery plaque levels, and the JAK2V617F mutation in these conditions are not well understood.

This study seeks to address this gap by evaluating NLR and artery plaque in people with Philadelphia negative MPNs, exploring how they relate to the JAK2V617F mutation. This research is pioneering in its focus on these specific associations.

Our study reports a mean age of 54.69 ±13.79 years for PV patients, 57.19 ± 12.07 years for ET patients, and 62.04 ± 12.97 years for MF patients, with an overall MPN patient group mean age of 57.7 ± 13.28 years and a gender distribution of 45.6% male. Previous studies have shown varying mean ages for MPN subtypes, often within similar ranges, though the precise figures can differ. For example, a study by **Tefferi et al.** .[15]

noted a median age at diagnosis of around 60 years for PV and ET pati-ents, with slightly older ages for MF, highlighting the similar trend of increasing age from PV and ET to MF. The gender distribution in our study is comparable to broader MPN demographics, where gender balance can vary but often does not show a strong predilection for either sex, contrary to specific cancers or blood disorders.

We found that the majority of MPN patients (78.9%) had a positive JAK2V617F mutation status. The JAK2V617F mutation is a key factor in the diagnosis and prognosis of PN-MPNs, with a high prevalence in these patients. [16]

The significant differences observed in routine laboratory data in our study between MPN patients and controls, especially in WBC count, N/L ratio, and other hematological and biochemical markers, highlight the systemic impact of MPNs. The observation that the N/L ratio was significantly higher in MPN patients with a positive JAK2V617F mutation (p=0.001) suggests that the presence of this mutation may be associated with a heightened state of inflammation or a different immune response. This could be due to the mutation driving a more aggressive disease phenotype, leading to an increased production of neutrophils or a relative decrease in lymphocytes.

Studies have demonstrated that the JAK2V617F mutation activates pathways that increase the production of inflammatory cytokines and growth factors, potentially explaining the observed elevation in the N/L ratio as a marker of systemic inflammation. [17, 18] This aligns with research indicating that the mutation may amplify the inflammatory environment in MPN patients, contributing to disease progression and symptomatology. [19]

In addition, **Şahin et al.** .[20]

study found that the presence of the JAK2V617F mutation typically associated with elevated levels of leukocytes, hemo-globin, and hematocrit, alongside a reduction in platelet count, contributing to a heightened risk of blood clots.

The prevalence of thrombosis in our MPN cohort was 37.8%. The prevalence of thrombosis in MPN varies, with **Rungjirajittranon et al.** [21] reporting an overall prevalence of 20%, and **Di Veroli et al**¨ [22] finding a low incidence of early thrombosis in the first 4 years after diagnosis. **Dentali et al**· [23] suggests a weak association between cerebral venous thrombosis and MPNs, indicating that not all patients with CVT require investigation for an underlying MPN. This finding suggests that while MPNs are a risk factor for thrombosis, their contribution to the risk of specific types of thrombosis like CVT may be limited.

Although the significant association of MPN patients in our study with increased carotid IMT and plaque scores compared to controls (p=0.024 for IMT and p=0.011 for plaque score) provides evidence of the elevated cardiovascular risk in this population, there was a significant correlation between thrombosis incidence and MPN patients with a positive JAK2V617F mutation. However, intima-media thickness (IMT) or and plaque score have no significant correlation with MPN patients with a positive JAK2V617F mutation. IMT is a measure used to assess the thickness of the carotid artery walls and is a marker of atherosclerosis and cardiovascular risk. A plaque score typically refers to the extent of atherosclerotic plaque buildup within the arteries. The absence of a correlation between the mutation status and cardiovascular risk parameters like IMT and plaque score might indicate that the mutation's impact is more confined to hematologic manifestations and inflammation rather than contributing directly to cardiovascular disease risk. However, this does not rule out the overall increased cardiovascular risk in MPN patients, which could be mediated by other mechanisms not directly related to the JAK2V617F mutation.

Several studies have consistently reported an increased risk of thrombosis and cardiovascular events in patients with myeloproliferative neopl-asms (MPNs), particularly those with the JAK2V-617F mutation. [24-26] **Borowczyk et al** [24]found that the relationship between the JAK2 V617F mutation's status and the proportion of affected cells has been linked to the likelihood of blood clot events in patients with PN-MPNs. Their findings indicate that individuals with over 20% of their cells carrying the JAK2 V617F mutation face a markedly higher risk of developing blood vessel-related issues, particularly venous blood clots· [25] Additionally, this mutation substantially increases thrombosis risk, notably in the presence of genetic predispose-itions to blood clotting· [26] The JAK2V617F muta-tion's occurrence also correlates with an increased frequency of clotting incidents among MPN pati-ents, serving as a significant, independent predictor of such events .[27] **Solli et al**· [28] demonstrated that a greater presence of the JAK2V617F mutation correlates with more severe coronary artery calcification in patients with MPNs. This connection holds even when taking into account other heart disease risk factors, indicating a direct relationship between the presence of JAK2V617F mutation and the development of coronary artery disease among these patients. However, the direct impact of JAK2-V617F on atherosclerotic markers is less clear, with findings varying across studies. This discrepancy could be due to differences in study populations, disease stages, or methodologies used to assess cardiovascular risk.

A study by **Solli et al**· [29] found that inflammatory risk factors, including NLR, are not associated with coronary artery calcification in patients with MPNs, indicating that the pathogenic mechanisms leading to cardiovascular complications in MPNs might be independent of systemic inflammation as measured by NLR.

Recent research indicates a connection between elevated frequencies of the JAK2V617F variant and the development of calcifications in the coronary arteries, rather than in the aortic valve, among patients with PN-MPNs, emphasizing the mutation's role in cardiovascular complications specific to coronary arteries· [30]

Yonal-Hindilerden et al [31]analyzed the clinical impact of JAK2V617F mutated allele burden in PN-MPNs, showing that higher allele burdens are

associated with disease severity manifestations and complications, including thrombosis.

Our study providing evidence that the NLR is a significant factor related to the inflammatory state in MPNs and is influenced by the JAK2V617F mutation. The N/L ratio could serve as a non-invasive biomarker to help in stratifying MPN patients based on their mutation status and possibly their risk of disease progression. It might also be useful in monitoring the disease course or response to therapy, especially in those with the JAK2V617F mutation. The association of MPNs with increased carotid plaque burden further supports the link between these hematologic malignancies and cardiovascular disease. However, the complex relationships among NLR, JAK2V617F mutation status, and carotid plaque burden suggest that the pathophysiology of cardiovascular risk in MPNs is multifactorial, involving genetic, hematologic, and inflammatory pathways.

Our study have some limitations. Firstly, the small sample size of our cohort. Secondly, the inherent nature of retrospective studies limits the ability to control for all potential confounding variables, which could influence the study outcomes. Prospective studies are needed to confirm these findings. Thirdly, being a single-center study may limit the generalizability of the findings to other populations or settings. Lastly, while the study accounted for age, gender distribution, and smoking status, other potential confounders such as diet, physical activity levels, and medication use were not controlled for or mentioned. These factors could influence the study outcomes.

Conclusion

Our study found a significant association between higher N/L ratios and the presence of the JAK2V617F mutation in patients with PN-MPNs. This suggests that the N/L ratio could serve as a marker of disease activity or mutation status in these patients. In addition, PN-MPN patients had significantly higher IMT and plaque scores compared to controls, indicating an increased burden of carotid plaque and possibly a higher risk of cardio-vascular events. However, no significant correlation was found between these markers and the JAK2V617F mutation status. In addition to the higher incidence of thrombosis was observed in MPN patients, there was a significant difference in thrombosis incidence between patients with positive and negative JAK2V617F mutation status. This suggests that factors beyond the JAK2V617F mutation may contribute to the risk of thrombosis in these patients.

Future research could benefit from prospective longitudinal studies to assess how changes in NLR over time correlate with cardiovascular outcomes in MPN patients, particularly in relation to JAK2V-617F mutation status. Additionally, explo-ring interventions that target inflammation and the JAK2/STAT pathway may provide insights into strategies to mitigate cardiovascular risk in this patient population.

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