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Prediction of Critical Limb Ischemia in Peripheral Arterial Disease by Comparing White Blood Cell to Mean Platelet Volume Ratio, Neutrophil to Lymphocyte Ratio and Platelet to Lymphocyte Ratio

Dr. Gaurav Mittal[1], Dr. V K Pandey[2], Dr. Kajal Mishra[3], Dr. Abhinav Jha[4]

Abstract: ***Background**: Peripheral arterial occlusive disease commonly referred to as peripheral arterial disease or peripheral vascular disease refer to the obstruction or deterioration of arteries other than those supplying the heart and within the brain. Peripheral arterial disease(PAD) is common and includes arterial part of vascular system except intra cranial and coronary arteries. Atherosclerosis is the main cause of PAD. Incidence of symptomatic PAD increases with age from approximately 0.3% per year for men aged 40 to 55 years to approximately 1% per year for men older than 75 years. **Method**: The study was carried out in the department of general surgery, Swaroop Rani Nehru hospital, Prayagraj. Study setting: All consecutive patients visiting the CTVS, plastic surgery and general surgery OPDs were selected who were fulfilling the criteria. **Results**: The Sensitivity of PLR, WMR and NLR was 95.65%, 93.48% and 89.13% respectively and the Specificity of PLR, WMR and NLR was 78.57%, 57.14% and 92.86% respectively for diagnosing PAOD. NLR, PLR, WMR had significant discriminatory power to predict critical limb ischemia. WMR (AUC 0.829; 95% CI: 0.690 to 0.924) was excellent and discriminatory power of NLR (AUC 0.788; 95% CI: 0.642 to 0.894) and PLR (AUC 0.793; 95% CI: 0.648 to 0.898) was acceptable. **Conclusion**: NLR, PLR, and WMR have significant discriminatory power to predict peripheral arterial disease and critical limb ischemia. Among all the parameters, platelet lymphocyte ratio is the best predictor of peripheral arterial disease. The sensitivity and specificity of all markers were comparable in terms of assessing CLI.*

Keywords: WBC to MPV ratio, WMR, Neutrophil lymphocyte ratio, NLR, Platelet-lymphocyte ratio, PLR, Critical Limb Ischemia, CLI, PAOD, peripheral arterial occlusive disease

1. Introduction

Peripheral arterial disease (PAD) is common and includes arterial part of vascular system except intra cranial and coronary arteries. Atherosclerosis is the main cause of PAD [1].

Incidence of symptomatic PAD increases with age from approximately 0.3% per year for men aged 40 to 55 years to approximately 1% per year for men older than 75 years. Nearly 75% of persons with Peripheral arterial occlusive disease (PAOD), of whatever age, have no symptoms [2]. Younger patients with PAOD are men, but the sexes are about equally represented among older patients. [3] PAD screening should be performed in adults over the age of 50 years with risk factors such as high cholesterol, hypertension, diabetes, smoking, obesity, family history of atherosclerosis, PAD or claudication, neuropathic leg pain, or a non-healing wound or infection on an extremity, in addition to anyone over the age of 70 years. [4, 5] Investigations include Duplex Doppler USG, Magnetic resonance angiography and compute tomographic angiography. The ankle brachial index (ABI) is a test that is used to facilitate diagnosis of Peripheral arterial disease(PAD), [6] calculated by dividing highest ankle SBP by highest arm SBP.

Among the inflammatory markers, the role of neutrophil lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR) and white blood cell to mean platelet volume ratio (WMR) has been explored in inflammatory diseases such as rheumatoid arthritis and ankylosing spondyloarhropathies. Its role is continuously been explored in PAD as well.

High NLR has been associated with high mortality in chronic limb ischemia (CLI) patients. [7] Rief et al, [8] have lately pointed out a relation between decreasing mean platelet volume (MPV) and CLTI. Guetl et al (2019) in study "The White Blood Cell Count to Mean Platelet Volume Ratio for the Prediction of Chronic Limb-Threatening Ischemia in Lower Extremity Artery Disease" concluded that there was significant association of an elevated WMR with the occurrence of CLTI in LEAD (Lower extremity artery disease) patients. [3]

Thus the study was conducted with the principal aim to determine association of white blood cells to mean platelet volume ratio (WMR), neutrophil-lymphocyte ratio (NLR) and platelet lymphocyte ratio (PLR) with critical limb ischemia in peripheral arterial occlusive disease (POAD).

Aims and Objective

1) To find correlation of WBC to MPV ratio (WMR), neutrophil lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR) to predict Critical Limb Ischemia (CLI) in PAOD.
2) To compare sensitivity and specificity of these three ratios for early diagnosis and management of patients with POAD.

2. Material and Method

Inclusion Criteria
Patients with symptoms of pain in the legs, weakness and claudication Patients with age >18 years

Both male and female patients Exclusion Criteria

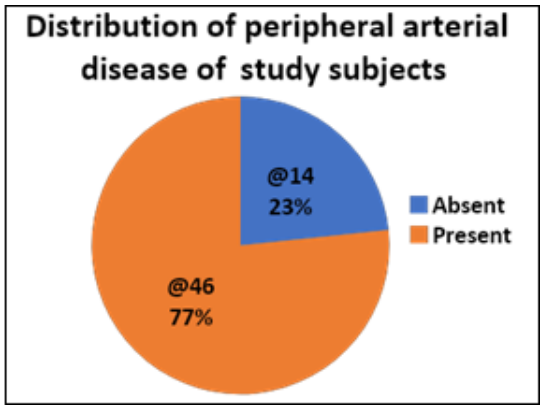
- Patients with Limb Ischemia due to any other causes such as trauma, venous ulcer, electric burn, thermal burn.
- All patients underwent clinical examination, ankle brachial index and Material and Methods 29 colour encoded duplex sonography for achieving a diagnosis of Peripheral arterial occlusive disease (PAOD) according to revised criteria as described in Trans-Atlantic Inter society Consensus document on management of peripheral arterial disease (TASC II). IX
- Patients on drugs like aspirin and clopidogrel
- Patients with lumbar claudication.

3. Results

We have taken total 60 patients in this study

Distribution of peripheral arterial disease of study subjects

Peripheral arterial disease	Frequency	Percentage
Absent	14	23.33%
Present	46	76.67%
Total	60	100.00%



In present study, in majority (76.67%) of patients, peripheral arterial disease was present. Peripheral arterial disease was absent in only 14 out of 60 patients.

Distribution of critical limb ischemia of study subjects

Critical limb ischemia	Frequency	Percentage
Absent	5	10.87%
Present	41	89.13%
Total	46	100.00%

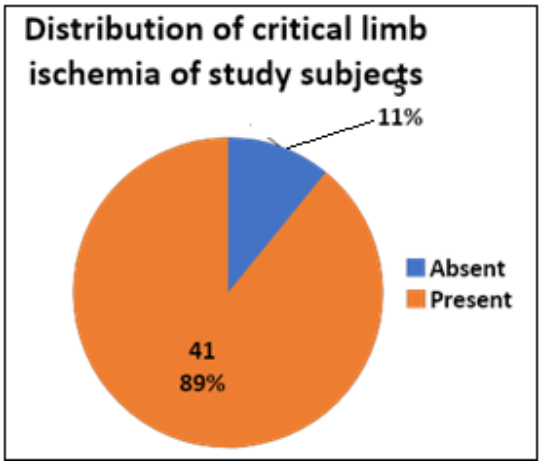


Figure 5: Distribution of critical limb ischemia of study subjects

In present study, in majority (89.13%) of patients, critical limb ischemia was present. Critical limb ischemia was absent in only 5 out of 46 patients.

Association with blood ratios- NLR, PLR, WMR with PAD

Table 13: Association of NLR, PLR and WMR with peripheral arterial disease

NLR, PLR and WMR	Absent (n=14)	Present (n=46)	Total	P value	Test performed
Neutrophil lymphocyte ratio					
<=4.7	13 (92.86%)	5 (10.87%)	18 (30%)	<.0001	Fisher Exact test
>4.7	1 (7.14%)	41 (89.13%)	42 (70%)		
Mean ± SD	3.57 ± 1.22	6.38 ± 1.58	5.72 ± 1.92	<.0001	Mann Whitney test;57
Median(IQR)	3.45 (2.488-4.575)	6.44 (6.075-7.158)	6.32 (4.575-6.808)		
Range	1.9-6.07	2.3-9.55	1.9-9.55		
Platelet lymphocyte ratio					
<=121	11 (78.57%)	2 (4.35%)	13 (21.67%)	<.0001	Fisher Exact test
>121	3 (21.43%)	44 (95.65%)	47 (78.33%)		
Mean ± SD	120.55 ± 25.06	175.92 ± 36.37	163 ± 41.29	<.0001	Mann Whitney test;57
Median(IQR)	110.5 (106.25-119)	171.5 (156.25-185.75)	166 (149.5-177.625)		
Range	99.7-169	111-337	99.7-337		
White blood cells to mean platelet volume ratio					
<=1.02	8 (57.14%)	3 (6.52%)	11 (18.33%)	0.0001	Fisher Exact test
>1.02	6 (42.86%)	43 (93.48%)	49 (81.67%)		
Mean ± SD	1.19 ± 0.44	1.61 ± 0.43	1.51 ± 0.47	0.002	t test;3.169
Median(IQR)	1.01 (0.84-1.55)	1.63 (1.302-1. 818)	1.56 (1.178-1.795)		
Range	0.67-1.89	0.7-2.69	0.67-2.69		

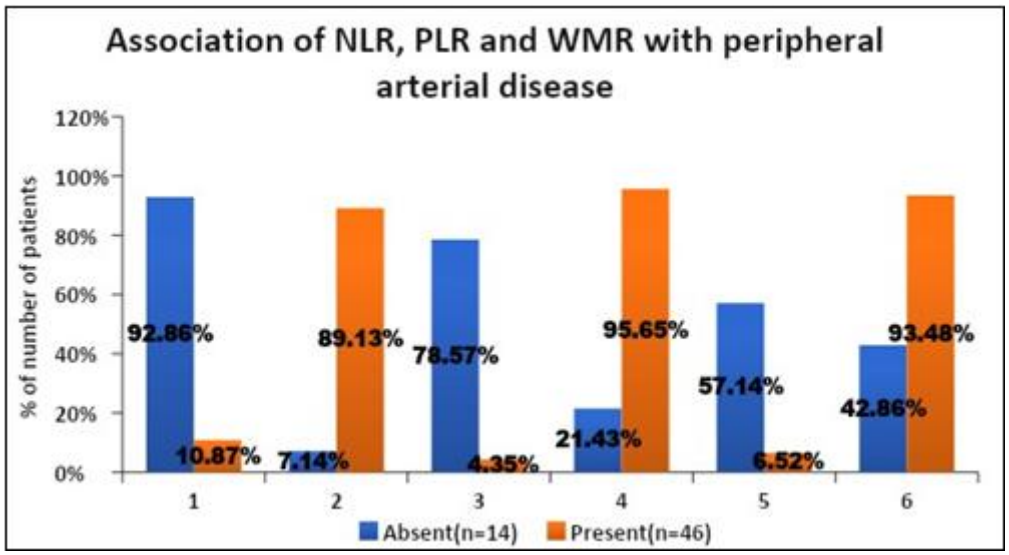


Figure 13: Association of NLR, PLR and WMR with peripheral arterial disease

Significant association was seen (p value<.05). NLR was <=4.7 in 92.86%) PLR was <=121 in 78.57% and WMR was <=1.02 in 57.14% of patients without peripheral arterial disease which was significantly higher as compared to patients with peripheral arterial disease (10.87%, 4.35%, 6.52) respectively. On the other hand, NLR was >4.7 in 89.13%, PLR was >121 in 95.65% and WMR was >1.02 in 93.48%, of patients with peripheral arterial disease which was significantly higher as compared to patients without peripheral arterial disease (7.14%, 21.43%, 42.86%) respectively.

Association of blood ratios with CLI

Table 17: Association of NLR, PLR and WMR with critical limb ischemia

NLR, PLR and WMR	Absent (n=5)	Present (n=41)	Total	P value	Test performed
Neutrophil lymphocyte ratio					
<=6.07	4 (80%)	8 (19.51%)	12 (26.09%)	0.013	Fisher Exact test
>6.07	1 (20%)	33 (80.49%)	34 (73.91%)		
Mean ± SD	5.18 ± 1.55	6.53 ± 1.54	6.38 ± 1.58	0.037	Mann Whitney test;43.5
Median(IQR)	5.26 (5.18-6.07)	6.54 (6.3-7.27)	6.44 (6.075-7.158)		
Range	2.65-6.75	2.3-9.55	2.3-9.55		
Platelet lymphocyte ratio					
<=156	4 (80%)	8 (19.51%)	12 (26.09%)	0.013	Fisher Exact test
>156	1 (20%)	33 (80.49%)	34 (73.91%)		
Mean ± SD	145.8 ± 30.94	179.6 ± 35.57	175.92 ± 36.37	0.034	Mann Whitney test;42.5
Median(IQR)	154 (120-156)	172 (161-186)	171.5 (156.25- 185.75)		
Range	111-188	137-337	111-337		
White blood cells to mean platelet volume ratio					
<=1.39	4 (80%)	10 (24.39%)	14 (30.43%)	0.025	Fisher Exact test
>1.39	1 (20%)	31 (75.61%)	32 (69.57%)		
Mean ± SD	1.14 ± 0.38	1.67 ± 0.41	1.61 ± 0.43	0.008	t test; 2.75
Median(IQR)	1.06 (0.8-1.39)	1.64 (1.44-1.82)	1.63 (1.302-1.818)		
Range	0.8-1.66	0.7-2.69	0.7-2.69		

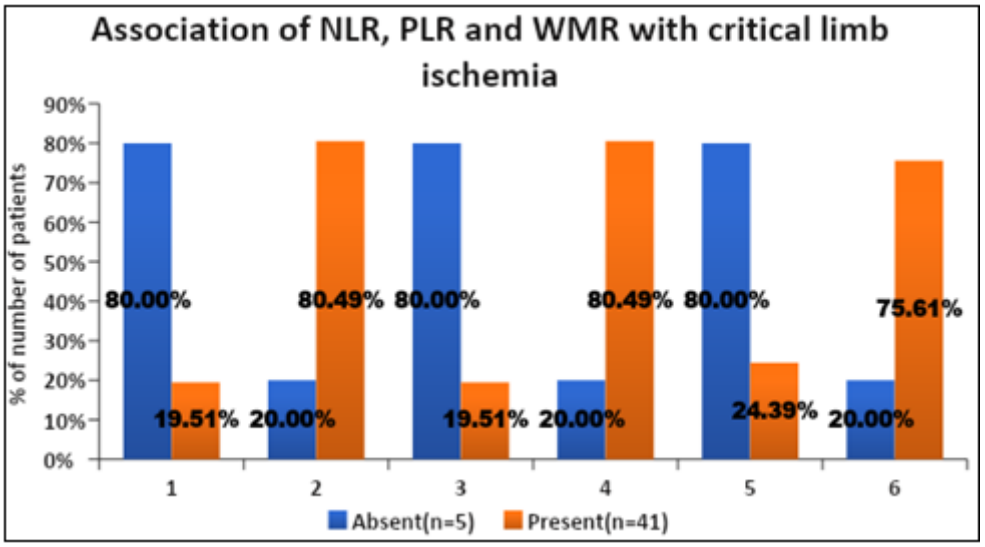


Figure 17: Association of NLR, PLR and WMR with critical limb ischemia

Significant association was seen with critical limb ischemia. (p value<.05). NLR was <=6.07 in 80% , PLR was <=156 in 80% , WMR was <=1.39 in 80% of patients without critical limb ischemia which was significantly higher as compared to patients with critical limb ischemia (19.51%, 19.51%, 24.39%) respectively. On the other hand, NLR was >6.07 in 80.49%, PLR was >156 in 80.49%, WMR was >1.39 in 75.61%, of patients with critical limb ischemia which was significantly higher as compared to patients without critical limb ischemia 20% each.

4. Discussion

Here in this study while assessing various non-invasive markers, we found that all the parameters (NLR, PLR, WMR) had significant discriminatory power to predict peripheral arterial disease. There was a significant association of NLR, WMR and PLR with PAOD such that the values of these markers were significantly higher in patients with PAOD as compared to those without PAOD. The Sn of PLR, WMR and NLR was 95.65%, 93.48% and 89.13% respectively and the Sp of PLR, WMR and NLR was 78.57%, 57.14% and 92.86% respectively for diagnosing PAOD. Among all the parameters, platelet lymphocyte ratio was the best predictor of peripheral arterial disease at cut off point of >121 with 91.10% chances of correctly predicting peripheral arterial disease.

We found that all the parameters (NLR, PLR, WMR) had significant discriminatory power to predict critical limb ischemia. Discriminatory power of white blood cells to mean platelet volume ratio (AUC 0.829; 95% CI: 0.690 to 0.924) was excellent and discriminatory power of neutrophil lymphocyte ratio (AUC 0.788; 95% CI: 0.642 to 0.894) and platelet lymphocyte ratio (AUC 0.793; 95% CI: 0.648 to 0.898) was acceptable. Neutrophil lymphocyte ratio and platelet lymphocyte ratio had sensitivity of 80.49% followed by white blood cells to mean platelet volume ratio (75.61%). On the other hand, neutrophil lymphocyte ratio, platelet lymphocyte ratio and white blood cells to mean platelet volume ratio had specificity of 80.00%. The Sn and Sp of all markers were comparable in terms of assessing CLI

Platelet lymphocyte ratio >121 was found to be the independent significant risk factors of peripheral arterial disease with adjusted odds ratio of 15.287.

5. Conclusion

In conclusion, NLR, PLR, and WMR have significant discriminatory power to predict peripheral arterial disease and critical limb ischemia. Among all the parameters, platelet lymphocyte ratio is the best predictor of peripheral arterial disease. The sensitivity and specificity of all markers were comparable in terms of assessing CLI.

Thus NLR, PLR, and WMR can be used as rapid, easily obtainable and cost-effective parameters to reliably identify PAOD patients and those at high risk for CLI. Selected patients may benefit from intensified medical treatment and the aggressive management of cardiovascular risk factors in order to prevent the progression of disease and a fatal outcome.

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