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Neutrophil-Lymphocyte Ratio, A Prognostic Indicator of Limb Survival in CLI Patients

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Abstract

Aims and Objectives: This study was designed to evaluate admission neutrophil-lymphocyte ratio in predicting risk of amputation in critical limb ischemia patients who could not get surgical or radiological (percutaneous transluminal angioplasty) revascularization.

Methods: A total of 150 patients presented with CLI to our hospital between June 2017 and June 2018 who could not have radiological or surgical revascularization are included in the study.Critical limb ischemia patients are those with is defined with ischemic rest pain and/or skin ulceration/gangrene in accordance to current guidelines reflecting patients with Fontaine class 3 and 4 . This is a comparative study, 75 with cli and rest pain and 75 without rest pain,so the NLR was significant in the rest pain group substantiated with the p value thus proving a vascular end point. .An optimal cut-off value for the continuous NLR was calculated by applying a receiver operating curve analysis to discriminate between CLI and non-CLI. In our study occurrence of CLI significantly increased with an increase in NLR. A P value <0.05 was considered statistically significant and the CI was 95%.Analyses were performed using SPSS software.

Results: Using an NLR cutoff of ≥3.2, the area under the receiver–operating characteristic curve was 0.71 (95% CI 0.54-0.78). Overall, there were a total of 9 (0.06%) deaths and 135(90%) amputations . The amputations were above ankle in 103 (77%) and below ankle in 32 (23%).

Conclusion: The neutrophil-lymphocyte ratio is an independent predictive factor for amputation in critical limb ischemia patients. An increased NLR is significantly associated with patients at high risk for CLI and other vascular endpoints.. Stratification of patients with CLI according to admission NLR should be considered in the limb survival analyses of future adjuvant and neoadjuvant trials to validate these findings.

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INTRODUCTION

Peripheral arterial occlusive disease is the obstruction or narrowing of the arteries supplying the peripheries. If untreated it can progress to critical limb ischemia where in the limb salvageability may be difficult. Hence PAOD must be promptly treated.

Critical limb ischemia (CLI) refers to arterial

occlusion causing marked reduction reduction in the blood flow to the extremities to a point causing rest pain, ulcers or even gangrene. It is a chronic condition which differentiates it from acute limb ischemia.

The risk factors for PAOD are hypertension, diabetes, smoking, dyslipidemia, hyperhomocysteinemia etc.

Also age plays an important risk factor, as the incidence of PAOD increases with increasing age. The incidence being 0.3% in men of age group 40-55 years and 1% in men above 75 years.

If PAOD is not diagnosed and treated timely, the patients are at a higher risk of developing complications like myocardial infarction or stroke. Critical limb ischemia patients are at a higher risk of developing generalized atherosclerotic disease.

Ankle brachial index (ABI) is simple indicator to diagnose critical limb ischemia. But in patients with mediasclerosis seen in oldage and diabetes, ABI becomes high due to stiffened arteries especially in the calf and ankle. Here the high ABI may not indicate a lowered perfusion to the extremity but only the stiffened arteries. Hence ABI is unreliable in patients with diabetes and oldage though these two factors are a high risk for CLI.

A high NLR has been shown to be associated with unfavourable outcomes in these circumstances. Poorer neurological outcome and increased mortality in stroke; increased mortality and major adverse cardiovascular events (MACE) in cases of acute myocardial infarction and increase in the morbidity and mortality of lower extremity artery disease. All these cases have been found to have an elevated NLR ratio.

This elevated NLR ratio indicates inflammation in the atherosclotic lesion. The increased neutrophils in the ratio is caused due to inflammation. These increased neutrophils release inflammatory mediators like arachidonic acid metabolites and platelet activating factors. This inflammatory stress causes cortisol induced stress response thus resulting in the relative reduction in lymphocyte count.

Thus this elevated NLR reflects an inflammatory state and hence associated with increased vascular endpoints like stroke, myocardial infarction or CLI.

MATERIAL AND METHODS

A total of 150 patients presented with CLI to our hospital between June 2017 and June 2018 who could not have radiological or surgical revascularization are included in the study. CLI is defined as PAOD patients presenting with ischemic rest pain and/or skin ulceration/gangrene in accordance to current guidelines reflecting patients with Fontaine class 3 and 4 .[5] This is a comparative study, 75 with cli and rest pain and 75 without rest pain,so the NLR was significant in the rest pain group substantiated with the p value thus proving a vascular end point. An optimal cut-off value for the continuous NLR was calculated by applying a receiver operating curve analysis to discriminate between CLI and non-CLI. In our study occurrence of CLI significantly increased with an increase in NLR.

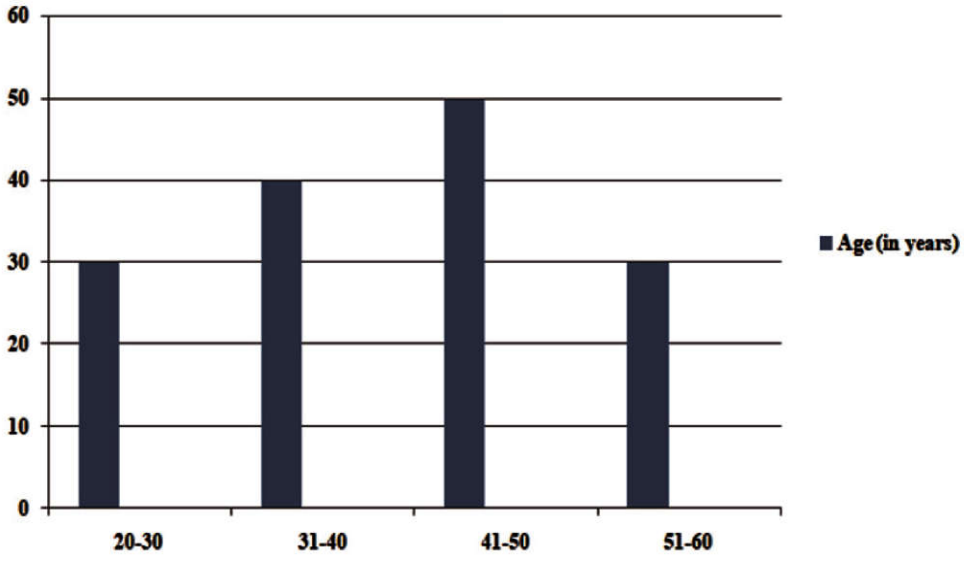

Fig. 1: Age distribution

The chart clearly shows the age distribution in our study with the maximum number of cases between the fourth and fifth decade of life, with the mean age being 45 years.

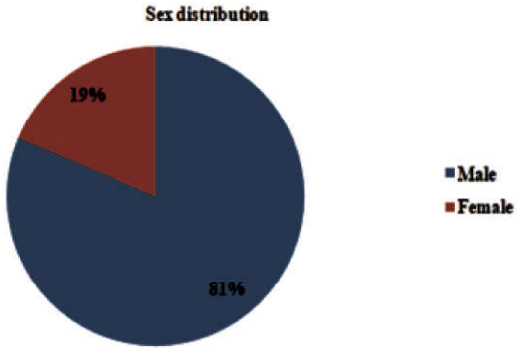

Fig. 2: Sex distribution

In our study, Males were affected more than females.

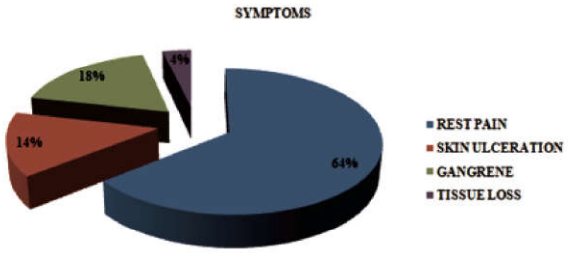

Fig. 3: Symptomology

RESULTS

Our study included 150 patients,

Group 1 – 75 in no, CLI without rest pain

Group 2 – 75 in no, CLI with rest pain.

Inclusion Criteria: Fontaine (Stage 3 & 4)

Rutherford (Grade 4, 5, 6)

Table 1: Results

Groups	Ampuation	Deaths	'P' Value
1	70	4	0.466
2	71	5	0.473

141 (94%) underwent Amputation and 9 (0.06%) deaths.

Using an NLR cutoff of 3.2, the area under the receiver operating characteristic curve was 0.71 (95% CI 0.54-0.78). A 'P' value <0.05 was considered statistically significant and the CI was 95%. Analyses were performed using SPSS software.

DISCUSSION

This study shows that NLR> 3.2 is associated with a higher risk of CLI in patients with PAOD

Pathophysiology:

Chronic inflammation is an important factor in peripheral arterial disease being both a causative factor and also the consequence of peripheral arterial disease. The NLR id derived from the ratio of neutrophils and lymphocytes. Inflammation causes increase in the neutrophil count. These increased neutrophils release inflammatory mediators like arachidonic acid and platelet activating factors. This inflammatory stress causes cortisol induced stress response thus resulting in the relative reduction in lymphocyte count.

As atherosclerosis progresses chances of limb ischemia increases. The study shows that an elevated NLR increases the risk of amputation in patients with peripheral vascular disease.

Risk stratification models which uses the existing clinical data helps to distinguish between good or bad candidates for surgical intervention. The patient's proinflammatory state also adds to this score.

In the study by Turak et al. It showed that there was an increase in risk of restenosis of coronary vessels following bare metal stents in patients with elevated NLR. They showed that NLR>2.73 predicted stent restenosis with a sensitivity of 80% and specificity of 75%. Elevated NLR in these patients shows the presence of inflammatory activity thus increasing the risk of restenosis.

PAOD is believed to be caused by active inflammation caused by the neutrophils releasing inflammatory mediators like arachidonic acid mediators, platelet activating factors, oxygen derived free radicals and hydrolytic enzymes like elastase, myeloperoxidase, acid phosphatises and other hydrolytic enzymes.

NLR is a proinflammatory marker. Elevated C reactive protein and NLR usually indicates a poor long term outcome in patients those who have undergone oncologic resections and those with cardiac disease.

The relation between the Fontaine stage and the NLR was studied in patients with PAOD. Haumer et al. did not find any significant association between the Fontaine stage and neutrophil count in patients with critical limb ischemia or intermittent claudication.

Clinically it is difficult to differentiate patients who are at high risk for CLI. Ankle brachial index as already mentioned is a good indicator but is only limited by mediasclerosis, thus not accurate in old patients and those suffering from diabetes. Where as NLR is a simple index which as per our study can predict the risk of developing CLI in patients with PAOD.

Classification	Stage	Clinical description
Fontaine	I	Asymptomatic
	IIa	Mild claudication
	IIb	Moderate-to-severe claudication
	III	Rest pain
	IV	Ulceration or gangrene
Rutherford	0	Asymptomatic
	1	Mild claudication
	2	Moderate claudication
	3	Severe claudication
	4	Rest pain
	5	Minor tissue loss
	6	Severe tissue loss or gangrene

Fig. 4: Fontaine and Rutherford Classification.

CONCLUSIONS

A advantages of NLR –

1. Inexpensive and easy to perform
2. Marker in predicting in hospital and long-term mortality.
3. Postoperative mortality.
4. Predictor of outcomes in percutaneous coronary intervention and coronary artery bypass grafting.
5. Predicting instent restenosis.

If NLR value is high, then it indicates poor prognosis and the patient is at high risk of developing CLI and other vascular endpoint deficit. The findings of the present study demonstrate that NLR obtained from a universally available low-cost test (CBC with differential) provide relevant information regarding the risk of amputation in patients who are admitted with nonreconstructable CLI.[10] Moreover, it is available preoperatively and may be of use in counseling patients with regard to treatment options and possible outcome.

High NLR is an excellent prognostic indicator in CLI patients. Stratification of patients with CLI according to admission NLR should be considered in the limb survival analyses of future adjuvant and neoadjuvant trials to validate these findings.

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