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Original Research Article

Comparative study between lymphocyte-monocyte ratio and platelet-lymphocyte ratio: novel markers for critical limb ischemia in peripheral arterial disease

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ABSTRACT

Background: Peripheral arterial occlusive disease (PAOD) is frequent and often not diagnosed in time. If treatment is not initiated early, disease progression and development of critical limb ischemia (CLI) is one possible complication. CLI is an entity with high mortality and high risk of limb amputation. As monocytes play a leading role in progression of atherosclerosis and platelets play a key role in atherosclerosis and atherothrombosis, we investigated lymphocyte-monocyte ratio (LMR), platelet lymphocyte ratio (PLR) and its association with CLI in peripheral arterial disease.
Methods: Retrospective observational study conducted between January 2015-December 2017 including 50 patients admitted in Rajarajeswari Medical College and Hospital, Bangalore. As an optimal cut-off value, a PLR of 150 and LMR of 5 were identified. Their association with CLI was noted.
Results: 50 patients with critical limb ischemia, stage 3 and 4 of Fontaine classification were included in this study. 72% patients had LMR less than 5.40% patients had PLR more than 150 and 36% patients had both LMR less than 5 and PLR more than 150. 96% patients with LMR<5 and 72% patients with PLR>150 underwent amputation.
Conclusions: An increased PLR and reduced LMR are significantly associated with patients at high risk for CLI. They are broadly available and cost effective. When done in early stage of the disease serves as a marker for CLI and aggressive treatment in such patients will reduce the risk of amputation.

Keywords: Critical limb ischemia, Platelet-lymphocyte ratio, Lymphocyte monocyte ratio, Peripheral arterial occlusive disease

INTRODUCTION

Peripheral arterial occlusive disease (PAOD) is frequent and often not diagnosed in time.[1] If treatment is not initiated early, disease progression and development of critical limb ischemia (CLI) is one possible complication.[2] CLI is an entity with high mortality and high risk of limb amputation. Although treatment options- especially endovascular treatment has improved in last decades, mortality and amputation rates are still high.[3,4] The incidence of CLI is approximately 500-1000 per million year and 25% of patients with CLI require major amputation. [5] Ankle brachial index can be used to distinguish CLI patients from non-CLI patients. ABI in patients with arteriosclerosis does not reflect true perfusion in the extremity measured, therefore it might be unreliable. Arteriosclerosis is also frequently found in elderly and diabetics, who are at the highest risk where

discrimination of CLI from non-CLI becomes difficult.[6] Atherogenesis is a chronic inflammatory process characterized by early leukocyte recruitment that continues throughout plaque maturation and rupture.[7,8] Indeed, WBC count elevation has been consistently associated with atherogenesis. However, different cell types amongst WBC have different pathogenic roles.[9,10] It is well known that neutrophil-lymphocyte ratio [NLR] was used as a marker to assess patients with atherosclerotic disease causing critical limb ischemia.[11] Lymphocytes were previously investigated as a part of NLR. However the role of Lymphocyte-monocyte ratio has been rarely investigated in assessing critical limb ischemia.

Objectives

The aim of the present study was to study the association of lymphocyte-monocyte ratio (LMR) with the presence of CLI in peripheral arterial disease, to study the association of platelet lymphocyte ratio (PLR) with the presence of CLI in peripheral arterial disease.

METHODS

A retrospective analysis was carried in Rajarajeswari Medical College and Hospital, Bangalore, India for a period of three years from Jan 2015 to December 2017.

Inclusion criteria

Patients admitted with peripheral arterial disease having critical limb ischemia, stage 3 and stage 4 of Fontaine classification.

Exclusion criteria

Gangrene due to any other cause.

Retrospective data from documents including sample reports of patients on the day of admission were collected in the following as white blood cell count and differential count like monocytes, lymphocytes and platelet count.

Statistical analysis

The Statistical software namely SPSS 18.0, and R environment ver.3.2.2 were used for the analysis of the data**.** Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SD (min-max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. Chi-square or Fisher exact test has been used to find the significance of study parameters on categorical scale between two or more groups, non-parametric setting for qualitative data analysis. LMR and PLR were calculated and the optimal cut-off values were calculated. Normal LMR-5 [lower limit of normal lymphocyte count (1 to 3×10^9/l) /normal monocyte count (0.2 to 1.0 $\times10^9$/l) i.e., 1/0.2=5][13]. Normal PLR-150 [lower limit of normal platelet count (150-450$\times10^9$/l) or normal lymphocyte count i.e., 150/1=150].[10,13]

RESULTS

A total of 50 patients with Critical limb ischemia, stage 3 and 4 of Fontaine classification were included in this study. There were 35 (70%) males and 15 (30%) female patients. Most commonly affected age group was found to be 50 to 70 years with mean age being 55.32 years. 36 (72%) patients had LMR less than 5.20 (40%) patients had PLR more than 150. 18 (36%) patients had LMR less than 5 and PLR more than 150. 50% patients underwent amputation. 18 (90%) patient with PLR>150 were found to be male, which was significant with p-0.012. 48% patients who underwent amputation were in the age group of 51 to 70 years and 92% of them were male. 24 (96%) patients with LMR<5 underwent amputation which is clinically significant, p value-<0.001. 18 (72%) patients with PLR>150 underwent amputation which is clinically significant, p value-<0.001.

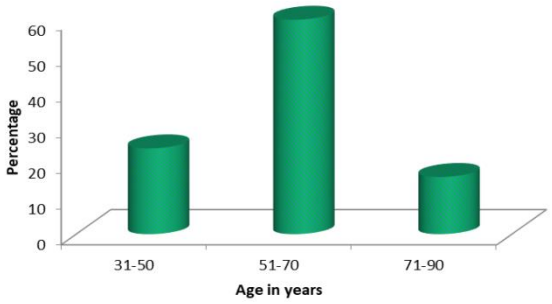

Figure 1: Age distribution of patients.

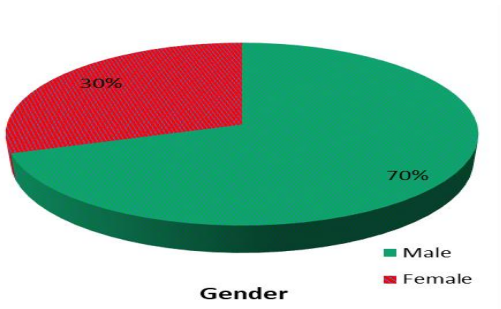

Figure 2: Gender distribution of patients.

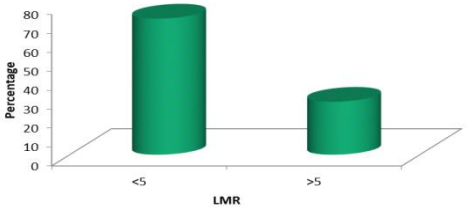

Figure 3: LMR distribution.

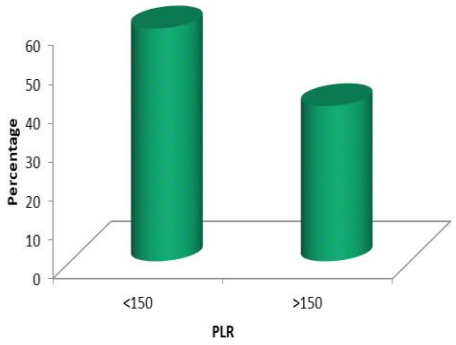

Figure 4: PLR distribution.

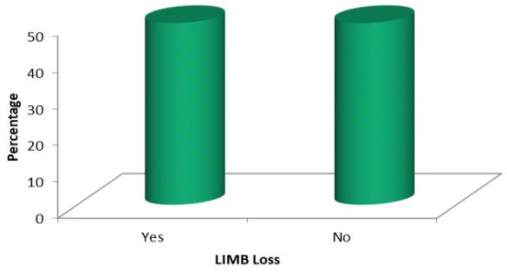

Figure 5: Limb loss distribution.

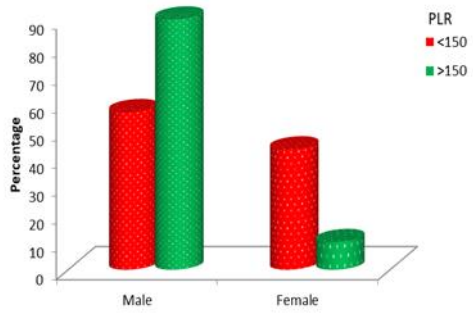

Figure 6: Gender distribution of patients studied in relation to PLR.

P=0.012*; Significant; Chi-Square test.

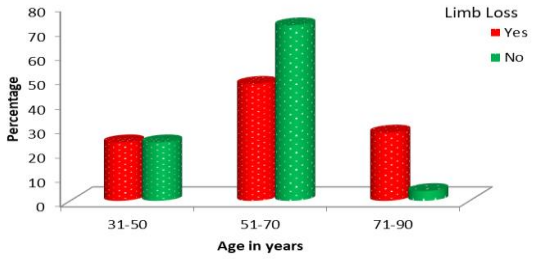

Figure 7: Age distribution of patients studied in relation to limb loss.

P=0.056*; Significant; Fisher exact test.

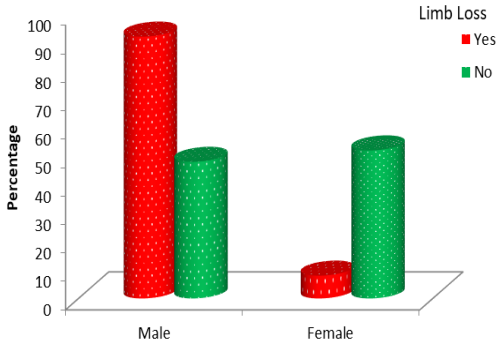

Figure 8: Gender distribution of patients studied in relation to limb loss.

P=0.001**; Significant; Chi-square test.

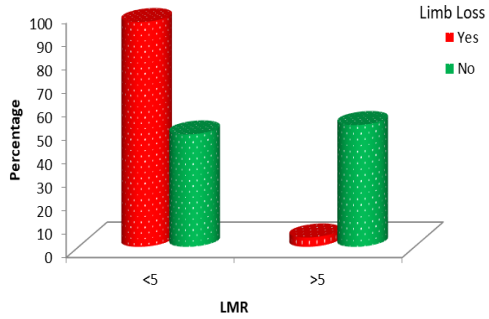

Figure 9: LMR distribution of patients studied in relation to limb loss.

P<0.001**; Significant; Chi-square test.

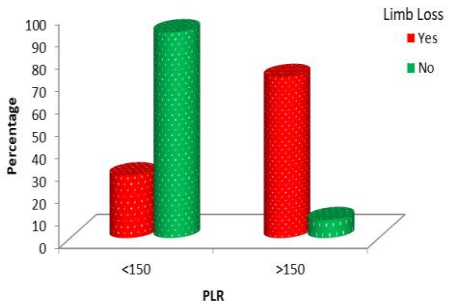

Figure 10: PLR distribution of patients studied in relation to limb loss.

P<0.001**; Significant; Chi-square test.

DISCUSSION

Multiple lines of evidence indicate that inflammation plays a pivotal role in atherogenesis, and that inflammatory markers such as WBC count may aid in the detection of individuals at higher atherosclerotic risk. In this study, PLR>150 and LMR<5 have shown significant

association with PAOD. By means of PLR, CLI patients with a high risk for limb amputation during a five year follow up period were discriminated from patients with a lower risk for limb amputation during the same follow up period.

Study by Nasir et al in 2005, concluded that monocytes were the only WBC type independently and significantly associated with PAD. Recently, the PLR has been published to enable the prediction of limb salvage in CLI patients.[12] One possible reason for this finding could be a change in blood viscosity due to higher and lower platelet counts leading to higher and lower PLR. Platelets further increase in case of inflammation as could be found in patients with active atherosclerosis leading to a more aggressive course of their disease. In our study the PLR also significantly correlated with LMR.

Platelets play an important role in the progression of atherosclerosis. According to current research platelets interact with endothelial cells and leukocytes and release inflammatory substances leading to adhesion and transmigration of monocytes.[13,14] These monocytes support inflammatory processes in the vessel wall promoting atherosclerotic lesions.[15] An elevated platelet count leading to an elevated PLR and elevated monocytes leading to decreased LMR might therefore lead to an increase in vascular endpoints. In our study, we were able to show that PLR>150 and LMR<5 was associated with vascular endpoints.

The second constituent of the PLR and LMR besides platelets and monocytes is the lymphocyte-count. Especially in CLI lymphocytes seem to play an important role in the clinical course of the disease. Iso et al investigated the role of implanted bone marrow cell composition on limb salvage in CLI patients.[16] In this study lymphocytes were significantly elevated in the limb salvage group.[16] One possible explanation for this finding is that lymphocytes might also be associated with the mediation of collateral growth via IL-16 secretion. This was shown recently in a murine hind limb ischemia model.[17] This might also be an explanation for our findings, as patients with a high lymphocyte count, leading to a lower PLR and higher LMR might have more collateral growth leading to less ischemia and therefore less CLI.

In a similar study by Gary et al in 2013, increased PLR>150 and decreased LMR<3.1 were significantly associated with high risk of CLI, but not the association with limb loss.[11] Where as in our study 72% of patients with PLR>150 and 96% of patients with LMR<5 were associated with limb loss. The main drawback of our study is the retrospective study design and that we used a single blood sample to calculate PLR and LMR. It therefore remains unclear whether this single blood sample reflects an elevated PLR and reduced LMR over time. Furthermore for exact stratification of the impact of PLR and LMR on future vascular events prospective studies are needed.

However, we were able to show that PLR>150 and LMR<5 can be used to discriminate patients at high risk for CLI from those with a low CLI-risk.

CONCLUSION

Though in our study, decreased LMR is more significantly associated with CLI compared to elevated PLR, elevated PLR and decreased LMR are significantly associated with limb loss in peripheral arterial occlusive disease.

Hence LMR and PLR done in the early stage of the disease serves as a marker for CLI and aggressive treatment in such patients will reduce the risk of amputation.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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