

Role of Neutrophil to Lymphocyte Ratio in Assessment of Prognosis in Patients with Diabetic Foot Infections.

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Abstract:

Background: Diabetic Foot Infections (DFI) are a major cause of significant morbidity and put a high economic burden on patients and health care facilities. The mortality rate due to diabetes and its related complications increased by 131% from 1990 to 2016. Neutrophil to lymphocyte ratio (NLR) is an indicator of physiological stress, immune response and systemic inflammation. Studies showed that NLR can predict the prognosis of various inflammatory conditions. In this study, we evaluated the value of NLR as a prognostic marker in DFI.

Materials and Methods: This prospective study was conducted on 265 patients admitted to S.V.R.R.G.G. Hospital, Tirupati, with the diagnosis of DFI, from March 2018 to March 2019. Patients with DFI were divided into tertiles based on the values of NLR at admission, a NLR of less than 4 as 1st tertile, a NLR of 4-8 as 2nd tertile and a NLR of more than 8 as 3rd tertile. The outcomes assessed were recovery by conservative management, requirement of debridement procedures, amputation, mortality and length of stay in the hospital in survivors.

Results: According to NLR values, patients in 3rd tertile had significantly high amputations (36%), high mortality (21%) and increased length of hospital stay in survivors (27±6 days) when compared with 1st tertile.

Conclusion: NLR is an easily available bedside biomarker and cost effective prognostic factor which can predict the outcome in diabetic foot infections. In this study, we established that high NLR is associated with a grave prognosis with high risk of amputation and mortality in diabetic foot infections.

Keywords: neutrophil to lymphocyte ratio, diabetic foot infections, prognosis amputation, mortality.

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I. Introduction

In India, about 70 million people suffer from diabetes, and the number is projected to rise to 125 million by 2040¹. The mortality rate due to diabetes and its related complications increased by 131% from 1990 to 2016². Foot infections are the commonest cause of hospitalisation in individuals with diabetes³. Diabetic Foot Infections (DFI) are a major cause of significant morbidity and put a high economic burden on patients and health care facilities⁴. The pathophysiology of DFI include neuropathy, vasculopathy and immunopathy⁵. DFI are a broad spectrum of conditions. Infectious diseases society of America (IDSA) provided a classification schema for the diagnosis of DFI⁴.

Table no 1: IDSA classification schema for diagnosis of DFI⁴.

Grade	Clinical description	Degree of infection
1	No purulence or evidence of inflammation	Uninfected
2	2 signs of inflammation ;such as pain or induration, cellulitis ,2 cm or less around ulcer; infection limited to skin and subcutaneous tissue	Mild
3	At least one of the following: cellulitis > 2cm around ulcer, lymphangitis, spread beneath fascia, abscess, gangrene, or involvement of muscle, tendon, or bone	moderate
4	Evidence of local infection as well as systemic toxicity, such as fever, hypotension, leucocytosis, or azotemia	Severe

Studies showed that changes in neutrophil and lymphocytes play an essential role in infection and inflammation³. Neutrophil to lymphocyte ratio is an indicator of physiological stress, immune response and systemic inflammation. Studies showed that NLR can predict the prognosis of various cancers⁶, coronary artery disease⁷, acute appendicitis⁸, diverticulitis⁹. Loonen et al.¹⁰. reported that NLR could be used as a predictor for bloodstream infections in the emergency care units. Kahramanca et al.¹¹ studied effectiveness of NLR, PLR with FGSI scores for prediction of number of debridements in Fournier’s gangrene and found that higher NLR and PLR values were associated with statistically significant increases in the number of debridements, duration of hospital stay, cost, and mortality rate. Taşoğlu et al.¹² studied the association of NLR and PLR with the limb survival in critical limb ischemia. Lou et al.¹³ showed patients with an NLR ≥ 3.8 are likely to suffer from amputation when compared to NLR < 3.8 . Yapıcı et al.¹⁴ reported that mean NLR is significantly higher in amputated group. Liu Y et al.¹⁵ investigated the mortality in patients with sepsis and found higher NLR with a cut-off value of 14.3 predicted higher mortality. Relationship of NLR with diabetes and its related complications has been studied¹⁶, but the prognostic ability of NLR has not been thoroughly evaluated. So we aimed to determine the prognostic ability of NLR in DFI.

II. Materials and Methods

This Prospective observational study included diabetic individuals, presenting with foot infections to department of general surgery, SVRR Government General Hospital, Tirupati between march 2018 to march 2019.

Study Design: Prospective observational study.

Study Location: This was a tertiary care teaching hospital based study done in department of general surgery, SVRR Government General Hospital, Tirupati, Andhra Pradesh.

Study Duration: march 2018 to march 2019

Sample size: 300 patients.

Sample size calculation: A total of 300 diabetic patients were enrolled for the study. Sample size was calculated by assuming confidence interval of 10%, confidence level of 95% and target population was 20000.

Subjects & selection method: The study population was drawn from consecutive diabetic patients who presented with foot infections to department of general surgery, SVRR Government General Hospital, Tirupati

Inclusion criteria :

- Diabetic Individuals presenting with foot infections with IDSA grade 2 to grade 4 (mild to severe infection).

Exclusion criteria

- Age less than 18 years and greater than 80 years,
- Prior history of cancers or under chemotherapy and autoimmune diseases.
- Prior history of chronic kidney disease and coronary artery disease.
- Deep vein thrombosis.
- Individuals not willing to participate in the study.

Procedure Methodology:

A total of 300 individuals were enrolled for the study, of whom 35 were excluded due to the above factors and the remaining 265 were included in the study. Our institutional ethical committee approved the study protocol. Informed consent was taken from all patients. No financial burden was kept on the patients.

Neutrophil to lymphocyte ratio is calculated by dividing neutrophil count with lymphocyte count.

$NLR = \text{neutrophil count} / \text{lymphocyte count}$.

Individuals were stratified into tertile model according to the neutrophil to lymphocyte ratio at the time of their admission.

Table no 2: Division based on value of NLR

1st TERTILE	2nd TERTILE	3rd TERTILE
NLR < 4	$4 \leq NLR < 8$ (4-8)	NLR ≥ 8

STATISTICAL ANALYSIS

The distribution of continuous variables were presented as means and standard deviations. The distribution of categorical variables were presented as frequencies and percentages. Log rank test was used to assess significance across the tertiles. A p value < 0.05 was considered statistically significant. All analyses were carried out by using SPSS v25 software.

III. Results

The study was conducted on 265 patients, who met with all the inclusion criteria and devoid of exclusion criteria and were stratified into tertiles according to NLR value at the time of admission.

Table no 3 : Incidence in tertile models of NLR.

NLR	1 st tertile(NLR <4)	2 nd tertile(4</=NLR<8)	3 rd tertile(NLR>/=8)
Number of patients(n=265)	84 (31.5%)	95 (36%)	86 (32.5%)
Mean NLR	2.9	6.7	13.1

As shown in table 3, 84 (31.5%) individuals had NLR < 4(1sttertile) with mean NLR 2.9.95(36%) individuals had NLR between 4-8 (2ndtertile) with mean NLR 6.7.86(32.5%) individuals had NLR greater than 8(3rdtertile) with mean NLR 13.1.

Table no 4: Demographic characteristics of study population.

	1 st tertile(NLR <4) N= 85	2 nd tertile(4</=NLR<8) N=95	3 rd tertile(NLR>/=8) N=86
Mean age(yrs)	45+/-9	47+/-8	54+/-7
Males	52(61%)	61(64%)	46(53%)
History of DM	63(74%)	85(89%)	80(93%)
History of HTN	43(50%)	51(53%)	45(52%)

As shown in table 4, the mean age of the study population was higher in the 3rdtertile. Male incidence was higher than female. Individuals with a previous history of diabetes were more than individuals with denovo diabetes. Individuals with history of hypertension was more in 2ndtertile. There was no significant statistical difference in above baseline characteristics

Table no 5: Assessment of outcomes in patients with DFI in tertile model.

Out come	1 st tertile(NLR <4) N= 85	2 nd tertile(4</=NLR<8) N=95	3 rd tertile(NLR>/=8) N=86	P value
Conservative management	60(70.65%)	27(28.5%)	7(8%)	0.03
Debridement/ drainage procedure	23(27%)	48(50.5%)	30(34.9%)	0.01
Amputation	2(2.35%)	14(14.7%)	31(36%)	0.01
Mortality	0	6(6.3%)	18(21.1%)	0.02
Length of hospital stay in survivors	5+/- 3	12 +/- 7	27 +/- 6	0.04

As shown in table 5, 70% of individuals in 1sttertile responded to conservative management compared to 28% in 2nd and 8% in 3rdtertile, indicating individuals with low NLR value can be managed conservatively. 50% in 2nd and 35% in 3rdtertile required debridement and drainage procedures when compared to 27% in 1sttertile. 36% in 3rdtertile underwent amputations when compared to 2.4% in 1sttertile, suggesting high NLR was more prone for amputations. Mortality was high in 3rdtertile (21%), when compared to 6% in 2ndtertile. There were no deaths in 1sttertile. Length of hospital stay was more in 3rdtertile (27±6 days) when compared to 2nd (12±7 days) and 1sttertile (5±3). All results were statistically significant. Statistically, Higher NLR was associated with higher amputation risk, high mortality and increased length of hospital stay.

IV. Discussion

The global prevalence of diabetes was 131 million in 2000, and it was estimated to increase to 366 million by 2030¹⁷. In developing nations like India, the burden of diabetes has risen steadily over the past quarter-century. In India, there were 65 million cases of diabetes in 2016 when compared to 26 million in 1990². Several factors such as irritation, inflammation, ischemia, neuropathy and infections contribute to the development of DFI¹⁴.

Neutrophils mediates the inflammatory response by mechanisms like release of arachidonic acid metabolites, cytotoxic oxygen – derived free radicals, myeloperoxidases, and various hydrolytic enzymes¹⁸. Lymphocytes are associated with mediation of collateral growth of vessels and also induces secretion of IL-16, which further promotes collaterogenesis¹⁹. This reduces ischemia which is one of the factor in development of DFI. NLR is a novel inflammatory marker which has been investigated for the prognostication of several diseases.

Kahramanca *et al.*¹¹ reported significantly higher NLR values in patients who required multiple debridement than in patients who required only one debridement in fouriers gangrene. Similar results were observed in the present study, higher NLR required more debridement and drainage procedures than individuals with low NLR group.

Lou *et al.*¹³ showed patients with an NLR ≥ 3.8 are likely to suffer from amputation when compared to NLR < 3.8 . In our study, we showed similar results where only 2% of patients undergoing amputations with NLR < 4 .

Yapici *et al.*¹⁴ reported that mean NLR is significantly higher in amputated group, concurring with results of the present study.

Liu Y *et al.*¹⁵ investigated the mortality in patients with sepsis and found higher NLR with a cutoff value of 14.3 predicted higher mortality. In our study, we found similar results, NLR > 8 had higher mortality rate. In our study, we showed NLR as an independent risk factor for amputation and mortality in DFI.

V. Conclusion

NLR is an easily available bedside biomarker and cost effective prognostic factor which can predict the outcome in diabetic foot infections. In this study, high NLR is significantly associated with greater requirement of debridement or drainage procedures, high amputation rate, high mortality and increased length of hospital stay indicating a grave prognosis.

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