*Original Article*

DOI: https://dx.doi.org/10.21088/ijmhs.2347.9981.5118.2

# Comaparative Study of Neutrophil Lymphocyte Ratio in Diabetic Patients with Foot Ulcer and without Foot Ulcer

**S.M. Goornavar[1], Sanganabasappa[2]**

IJMHS (January-June 2018) 05 (1): 11-15 / ©Red Flower Publication Pvt. Ltd.

**Abstract**

*Objective:* Diabetes, is fast growing the status of potential epidemic in India with more than 62 millions diabetic individuals currently diagnosed with disease [1]. Over 85% of lower limb amputations are preceded by foot ulcer and diabetes remains the major cause of non-traumatic amputation across the world with rates being as much as 15 times higher than in non-diabetic population. *Method:* Diabetic patients aged above 18 years with(cases) and without (controls) foot ulcer admitted in H.S.K Hospital during the study period i.e., from 1st Janvary 2016 to 30th June 2016. *Statistical analysis:* Data was analyzed statistically by Mean, Standard Deviation, proportions, Chi square test and other relevant statistical tests using SPIS Softwares. *Result:* There is statistically significant correlation between DFU and NLR with a p value 0.000 which shows high level of significance. *Conclusion:* NLR can be directly calculated from the neutrophil and lymphocyte counts and can be easily be obtained from a complete blood cell count on admission and during follow up. Thus increasing values of NLR during follow up can be used to predict sub clinical inflammation and impending complications like DFU.

**Keywords:** Neutrophil to Lymphocyte Ratio, Diabetic Foot Ulcer

**Author's Affiliation:** [1]Professor [2]Junior Resident, Department of Medicine, S Nijalingappa Medical College, HSK (Hanagal Shree Kumareshwar) Hospital and Research Centre, Bagalkot, Karnataka 587102, India.

**Corresponding Author: Sanganabasappa,** Junior Resident, Department of Medicine, S Nijalingappa Medical College, HSK (Hanagal Shree Kumareshwar) Hospital and Research Centre, Bagalkot, Karnataka 587102, India.
E-mail: dr.sanju.nh@gmail.com

**Received on** 03 April 2018
**Accepted on** 23 April 2018



## Introduction

Diabetes, is fast growing the status of potential epidemic in India with more than 62 millions diabetic individuals currently diagnosed with disease [1]. Over 85% of lower limb amputations are preceded by foot ulcer and diabetes remains the major cause of non-traumatic amputation across the world with rates being as much as 15 times higher than in non-diabetic population. "Prevention is the first step towards slowing diabetic foot problem" and it is estimated that upto 85% of all amputations in diabetes should be preventable [3]. In recent years it is emphasised that an active inflammation occurs in the pathogenesis of diabetes mellitus and its complications such as atheroscleosis and neutrophil to lymphocyte ratio being suggested as an indicator of subclinical inflammation –it could be possible to find an association between neutrophil to lymphocyte ratio and micro and macrovascular complications of diabetes mellitus [4,5]. So our study aims at analysing association between neutrophil to lymphocyte ratio (as a marker of sub clinical inflammation ) and diabetic foot ulcer (a complication secondary to micro and macrovasculopathy)- so that neutrophil to lymphocyte ratio–an economical and easy accessible investigation could be used as a predictor of diabetic complication such as foot ulcer and also for follow up of already diagnosed case.

Aim of this study is to study the relationship between diabetic foot ulcer and neutrophil to lymphocyte ratio as a marker of subclinical inflammation.

## Methodology

*Source of data:* Diabetic patients aged above 18 years with(cases) and without(controls) foot ulcer admitted in H.S.K Hospital during the study period i.e., from 1st Janvary 2016 to 30th June 2016.

***Methods of collection of data***

*Inclusion criteria for cases with DFU*

1. Both male and female diabetic patients diagnosed as per ADA criteria presenting with foot ulcer.

2. The patients aged more than 18 years.

*Inclusion criteria for cases without DFU*

1. Both male and female diabetic patients diagnosed as per ADA criteria presenting without foot ulcer.

2. The patients aged more than 18 years.

*Exclusion criteria for the cases with DFU*

Diabetic patients with foot ulcer with the following criteria will be excluded

1. active infection,

2. leucocytosis,

3. malignancy,

4. who are using steroid without any reason.

5. systemic infection.

*Exclusion criteria for the cases without DFU*

Diabetic patients without foot ulcer with the following criteria will be excluded

1. systemic infection,

2. leucocytosis,

3. malignancy,

4. who are using steroid without any reason.

*Study design:* An observational study.

*Sample size:* Sample size calculation was done using openepi software, version 2.3.1.

At 95% confidence levels and 80% power of the study.

Mean difference of NLR ratio of 2 was considered as clinically relevant, with known standard deviations from the previous study was used for calculation [7].

At the ratio of 1:2, cases and controls required for the sample size calculation is-

Cases with DFU=31 which can be rounded off to 36

Cases without DFU=31, which can be rounded off to 36

Hence sample size for the study is 72.

*Ethical clearance:* In compliance with the requirements of International Conference on Harmonisation(ICH) related to Good Clinical Practice (GCP) Schdule Y, research protocol, information sheet and other related documents submitted to Institutional ethics committee of SNMC and clearance for the conduction of study got approved.

*Statistical analysis:* Data was analyzed statistically by Mean, Standard Deviation, proportions, Chi square test and other relevant statistical tests using SPIS Softwares.

$p < 0.05$ is considered significant.

**Results**

In our study as per statistical analysis interpreted in above table

Mean Neutrophil to Lymphocyte Ratio (NLR) is **3.888** for cases.

**Table 1:** Age ,period of disease and group wise distribution of participants

| Age | Group | | | Period of Disease | | | | |
|---|---|---|---|---|---|---|---|---|
| | DFU | DM no DFU | Total | 0-5 | 6-10 | 11-15 | 16-20 | Total |
| 41-45 | 1 | 1 | 2 | 0 | 3 | 0 | 0 | 3 |
| 46-50 | 7 | 7 | 14 | 18 | 3 | 0 | 0 | 21 |
| 51-55 | 2 | 2 | 4 | 3 | 3 | 0 | 0 | 6 |
| 56-60 | 10 | 10 | 20 | 6 | 24 | 0 | 0 | 30 |
| 61-65 | 4 | 4 | 8 | 0 | 9 | 3 | 0 | 12 |
| 66-70 | 8 | 8 | 16 | 0 | 18 | 3 | 3 | 24 |
| 71-75 | 3 | 3 | 6 | 0 | 0 | 6 | 3 | 9 |
| 76-80 | 1 | 1 | 2 | 0 | 0 | 3 | 0 | 3 |
| Total | 36 | 36 | 72 | 18 | 40 | 10 | 4 | 72 |

**Table 2:** Group statistics

| Parametre | Group | Number | Mean | Std. Deviation | T-test for equality of means | |
|---|---|---|---|---|---|---|
| | | | | | t | P |
| Total count | Case | 36 | 9386.11 | 1483.654 | -2.10 | 0.039 |
| | Control | 36 | 8494.44 | 2066.874 | | |
| Neutrophil | Case | 36 | 74.97 | 6.872 | -6.90 | 0.000 |
| | Control | 36 | 62.11 | 10.634 | | |
| Lymphocyte | Case | 36 | 21.61 | 6.133 | 5.899 | 0.000 |
| | Control | 36 | 32.92 | 9.726 | | |
| Neutrophil-lymphocyte ratio | Case | 36 | 3.887908 | 1.5845659 | -5.43 | 0.000 |
| | Control | 36 | 2.160106 | 1.0642727 | | |

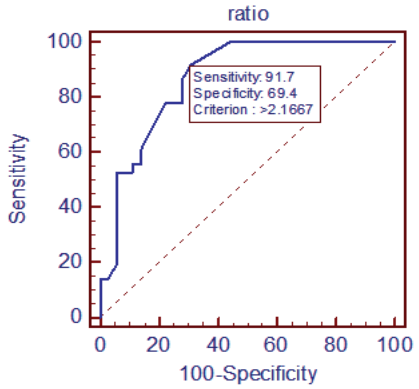
MeanNeutrophil to Lymphocyte Ratio (NLR) is **2.160** for controls.

There is statistically significant correlation between DFU and NLR with a p value 0.000 which shows high level of significance.

### Roc curve

The best cut-off value for Neutrophil-Lymphocyte ratio in cases was found to be 2.16 with the Sensitivity of 91.7 and Specificity of 69.4.

The area under curve for Neutrophil-Lymphocyte ratio is 0.868 which is statistically significant (p<0.0001).




### Discussion

*Neutrophil-Lymphocyte Ratio as a marker of subclinical inflammation*

Neutrophil lymphocyte ratio Neutrophil to lymphocyte ratio (NLR) is a new addition to the long list of the inflammatory markers. NLR, which is calculated from complete blood count with differential, is an inexpensive, easy to obtain, widely available marker of inflammation, Previous studies have demonstrated that leukocyte subtype, and neutrophil-lymphocyte ratio are indicators of systemic inflammation. Eman Youssef et al. [6]. conducted a study called" Relationship Between Neutrophil-Lymphocyte Ratio and Microvascular Complications in Egyptian Patients with Type 2 Diabetes". The study aimed to evaluate the relationship between diabetic microvascular complications, namely diabetic retinopathy, nephropathy, neuropathy, and neutrophil-lymphocyte ratio in type 2 diabetic patients.

Based on the results of this study, they could conclude that neutrophil-lymphocyte ratio (NLR), which is an efficient, simple and stable marker of inflammation, can serve as an important predictor for the presence of microvascular complications in Egyptian patients with type 2 diabetes.

James Ian Park et al. [7] conducted a study titled "An elevated neutrophil-lymphocyte ratio independently predicts mortality in chronic critical limb ischemia". In their study all patients admitted to a single vascular unit with chronic critical limb ischemia were identified prospectively over a 2-year period starting from January 2005.

And they concluded that an elevated NLR can identify a poor-risk subset of patients among those being treated for critical limb ischemia. This simple, inexpensive test may, therefore, add to risk stratification of these high-risk patients.

Many epidemiological studies have determined that DM is associated with chronic inflammation [8], which may contribute to the acceleration of

diabetic microangiopathy and the development of macroangiopathy, patients with Type 2 DM are in a state of low-degree chronic inflammation that induces hyper secretion of inflammatory factors, such as CRP, IL-6, TNF-α, and MCP-1, which results in a constantly elevated neutrophilic granulocyte count .

NLR can easily be calculated using the neutrophil-tolymphocyte ratio in peripheral blood count. Calculating NLR is simpler and cheaper than measuring other inflammatory cytokines, such as IL-6, IL-1β and TNF-α. Recent studies have shown that NLR as microvascular complications of diabetes is related with the presence of nephropathy and it has been correlated as an indicator of end stage renal failure with albuminuria levels.

Neutrophils mediate inflammatory response by numerous mechanisms, such as release of arachidonic acid metabolites and platelet aggravating factors, cytotoxic oxygen derived free radicles, and hydrolytic enzymes such as myeloperoxidase, elastase, various hydrolytic enzymes and acid phosphatases. The NLR therefore reflects both the neutrophilia of inflammation and the relative lymphopenia of crtisol induced stress response.

*Neutrophil-Lymphocyte ratio in diabetic foot ulcer*

While we revieved literature, studies about association of NLR with diabetic foot ulcers were comparatively rare. Previous studies show that diabetes mellitus and its complications are associated with subclinical inflammation and NLR could be used as a marker of subclinical inflammation.Since DFU is a significant macrovascular complication we intended to study association of NLR with DFU.

So we conducted an observational study with 36 cases (with DFU) and 36 diabetic patients without foot ulcer. The results of our study showed that mean NLR in cases was 3.888 and that in control was 2.160.

So mean NLR in cases was significantly higher in cases compared to controls and p value for association of NLR with DFU was 0.000 (< 0.05) inferring a statistically significant association.

Thus our study proved a positive correlation between NLR and DFU.

Since NLR is a marker of systemic sub clinical inflammation determining NLR in the presence of high levels of diabetic foot ulcers is not a local inflammation alone but also showed that there is a systemic inflammatory response.

In patients with diabetic foot, other macrovascular complications of diabetes can be seen much more and using NLR has been suggested as an economical and accessible inflammatory markers for developing and following of macrovascular complication. In this regard, more extensive and more studies with more several patients are needed.

Hence neutrophil lymphocyte ratio can be useful marker in diabetic patients to predict micro and macrovascular complications.

## Conclusion

A risk stratification model is an important clinical tool that uses existing clinical data to predict a patient's prognosis and provides a rational discrimination between risky and non risky patients.

NLR can be directly calculated from the neutrophil and lymphocyte counts and can be easily be obtained from a complete blood cell count on admission and during follow up. Thus increasing values of NLR during follow up can be used to predict sub clinical inflammation and impending complications like DFU.

NLR is also stable and resistant to environmental and physiologic changes, such as dehydration, physical activity, and blood sample handling, that affect the results of other markers.

*Recommendations*

NLR could be used as an economical and accessible inflammatory markers for developing and following of macrovascular complications, in particular foot ulcer.In this regard, more extensive and more studies with more several patients are needed.

*Limitations of study*

1. Study involves limited population. So to make the results generalized studies with large number of population should be conducted.

2. NLR could be raised in conditions other than foot ulcer like nephropathy, heart failure ,insulin resistance, atherosclerosis etc. So broad defferentials to be kept in mind to make NLR as a predictive for Diabetic foot ulcer.

## References


1. Joshi SR, Parikh RM. India-Diabetic capital of the world: now heading towards hypertension. J Assoc Physicians India 2007;55:323-4.
2. Singh N, Armstrong DG, Lipsky BA. Preventing foot ulcer in patients with diabetes. JAMA 2005;293: 217-28.
3. Boulton AJM, Vileikyte L, Ragnorson-Tennvall G, Apelquist J. The global burden of diabetic foot disease. Lancet 2005;366:1719-24.
4. Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004;27:813-23.
5. Uthamalingam S, Patvardhan EA, Subramanian S. Utility of the Neutrophil to Lymphocyte Ratio in Predicting Long-Term Outcomes in Acute Decompensated Heart Failure. Am J Cardiol 2011;107(3):433-8.
6. Eman Youssef Moursy, Magdy Helmy Megallaa, Reham Fadl Mouftah, Soha Magdy Ahmed. Relationship Between Neutrophil-Lymphocyte Ratio and Microvascular Complications in Egyptian Patients with Type 2 Diabetes. American Journal of Internal Medicine 2015;3(6):250-55.
7. James Ian Spark, Janahan Sarveswaran, Nadia Blest, Peter Charalabidis, Sonal Asthana. An elevated neutrophil-lymphocyte ratio independently predicts mortality in chronic critical limb ischemia. J Vasc Surg 2010;52(3):632–36.
8. Imtiaz F, Shafique K, Vart P, Rao S. Neutrophil lymphocyte ratio as a measure of systemic inflammation in prevelent cronic diseases in Asian population. Int Arch Med 2012;5:2.

*Revised Rates for 2018 (Institutional)*

| Title of the Journal | Frequency | India(INR) Print Only | India(INR) Online Only | Outside India(USD) Print Only | Outside India(USD) Online Only |
|---|---|---|---|---|---|
| Community and Public Health Nursing | Triannual | 5500 | 5000 | 430 | 391 |
| Dermatology International | Semiannual | 5500 | 5000 | 430 | 391 |
| Gastroenterology International | Semiannual | 6000 | 5500 | 469 | 430 |
| Indian Journal of Agriculture Business | Semiannual | 5500 | 5000 | 413 | 375 |
| Indian Journal of Anatomy | Bi-monthly | 8500 | 8000 | 664 | 625 |
| Indian Journal of Ancient Medicine and Yoga | Quarterly | 8000 | 7500 | 625 | 586 |
| Indian Journal of Anesthesia and Analgesia | Monthly | 7500 | 7000 | 586 | 547 |
| Indian Journal of Biology | Semiannual | 5500 | 5000 | 430 | 391 |
| Indian Journal of Cancer Education and Research | Semiannual | 9000 | 8500 | 703 | 664 |
| Indian Journal of Communicable Diseases | Semiannual | 8500 | 8000 | 664 | 625 |
| Indian Journal of Dental Education | Quarterly | 5500 | 5000 | 430 | 391 |
| Indian Journal of Diabetes and Endocrinology | Semiannual | 8000 | 7500 | 597 | 560 |
| Indian Journal of Emergency Medicine | Quarterly | 12500 | 12000 | 977 | 938 |
| Indian Journal of Forensic Medicine and Pathology | Quarterly | 16000 | 15500 | 1250 | 1211 |
| Indian Journal of Forensic Odontology | Semiannual | 5500 | 5000 | 430 | 391 |
| Indian Journal of Genetics and Molecular Research | Semiannual | 7000 | 6500 | 547 | 508 |
| Indian Journal of Hospital Administration | Semiannual | 7000 | 6500 | 547 | 508 |
| Indian Journal of Hospital Infection | Semiannual | 12500 | 12000 | 938 | 901 |
| Indian Journal of Law and Human Behavior | Semiannual | 6000 | 5500 | 469 | 430 |
| Indian Journal of Legal Medicine | Semiannual | 8500 | 8000 | 607 | 550 |
| Indian Journal of Library and Information Science | Triannual | 9500 | 9000 | 742 | 703 |
| Indian Journal of Maternal-Fetal & Neonatal Medicine | Semiannual | 9500 | 9000 | 742 | 703 |
| Indian Journal of Medical & Health Sciences | Semiannual | 7000 | 6500 | 547 | 508 |
| Indian Journal of Obstetrics and Gynecology | Bi-monthly | 9500 | 9000 | 742 | 703 |
| Indian Journal of Pathology: Research and Practice | Monthly | 12000 | 11500 | 938 | 898 |
| Indian Journal of Plant and Soil | Semiannual | 6500 | 6000 | 508 | 469 |
| Indian Journal of Preventive Medicine | Semiannual | 7000 | 6500 | 547 | 508 |
| Indian Journal of Research in Anthropology | Semiannual | 12500 | 12000 | 977 | 938 |
| Indian Journal of Surgical Nursing | Triannual | 5500 | 5000 | 430 | 391 |
| Indian Journal of Trauma and Emergency Pediatrics | Quarterly | 9500 | 9000 | 742 | 703 |
| Indian Journal of Waste Management | Semiannual | 9500 | 8500 | 742 | 664 |
| International Journal of Food, Nutrition & Dietetics | Triannual | 5500 | 5000 | 430 | 391 |
| International Journal of Neurology and Neurosurgery | Quarterly | 10500 | 10000 | 820 | 781 |
| International Journal of Pediatric Nursing | Triannual | 5500 | 5000 | 430 | 391 |
| International Journal of Political Science | Semiannual | 6000 | 5500 | 450 | 413 |
| International Journal of Practical Nursing | Triannual | 5500 | 5000 | 430 | 391 |
| International Physiology | Triannual | 7500 | 7000 | 586 | 547 |
| Journal of Animal Feed Science and Technology | Semiannual | 7800 | 7300 | 609 | 570 |
| Journal of Cardiovascular Medicine and Surgery | Quarterly | 10000 | 9500 | 781 | 742 |
| Journal of Forensic Chemistry and Toxicology | Semiannual | 9500 | 9000 | 742 | 703 |
| Journal of Global Medical Education and Research | Semiannual | 5900 | 5500 | 440 | 410 |
| Journal of Global Public Health | Semiannual | 12000 | 11500 | 896 | 858 |
| Journal of Microbiology and Related Research | Semiannual | 8500 | 8000 | 664 | 625 |
| Journal of Nurse Midwifery and Maternal Health | Triannual | 5500 | 5000 | 430 | 391 |
| Journal of Orthopedic Education | Triannual | 5500 | 5000 | 430 | 391 |
| Journal of Pharmaceutical and Medicinal Chemistry | Semiannual | 16500 | 16000 | 1289 | 1250 |
| Journal of Plastic Surgery and Transplantation | Semiannual | 26400 | 25900 | 2063 | 2023 |
| Journal of Practical Biochemistry and Biophysics | Semiannual | 7000 | 6500 | 547 | 508 |
| Journal of Psychiatric Nursing | Triannual | 5500 | 5000 | 430 | 391 |
| Journal of Social Welfare and Management | Triannual | 7500 | 7000 | 586 | 547 |
| Medical Drugs and Devices Research | Semiannual | 2000 | 1800 | 156.25 | 140.63 |
| New Indian Journal of Surgery | Bi-monthly | 8000 | 7500 | 625 | 586 |
| Ophthalmology and Allied Sciences | Triannual | 6000 | 5500 | 469 | 430 |
| Otolaryngology International | Semiannual | 5500 | 5000 | 430 | 391 |
| Pediatric Education and Research | Triannual | 7500 | 7000 | 586 | 547 |
| Physiotherapy and Occupational Therapy Journal | Quarterly | 9000 | 8500 | 703 | 664 |
| RFP Indian Journal of Medical Psychiatry | Semiannual | 8000 | 7500 | 625 | 586 |
| RFP Journal of Gerontology and Geriatric Nursing | Semiannual | 5500 | 5000 | 430 | 391 |
| Urology, Nephrology and Andrology International | Semiannual | 7500 | 7000 | 586 | 547 |

**Terms of Supply:**

1. Agency discount 10%. Issues will be sent directly to the end user, otherwise foreign rates will be charged.
2. All back volumes of all journals are available at current rates.
3. All Journals are available free online with print order within the subscription period.
4. All legal disputes subject to Delhi jurisdiction.
5. Cancellations are not accepted orders once processed.
6. Demand draft / cheque should be issued in favour of "**Red Flower Publication Pvt. Ltd.**" payable at **Delhi**
7. Full pre-payment is required. It can be done through online (http://rfppl.co.in/subscribe.php?mid=7).
8. No claims will be entertained if not reported within 6 months of the publishing date.
9. Orders and payments are to be sent to our office address as given above.
10. Postage & Handling is included in the subscription rates.
11. Subscription period is accepted on calendar year basis (i.e. Jan to Dec). However orders may be placed any time throughout the year.

**Order from**

Red Flower Publication Pvt. Ltd., 48/41-42, DSIDC, Pocket-II, Mayur Vihar Phase-I, Delhi - 110 091 (India),
Mobile: 8130750089, Phone: 91-11-45796900, 22754205, 22756995 E-mail: sales@rfppl.co.in, Website: www.rfppl.co.in