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Role of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in Diabetic Ulcer Patients

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Abstract: ***Diabetic ulcers are a common occurrence in diabetic patients but remain a challenge with regard to scoring, prediction of outcome and planning of appropriate treatment plan. NLR is a novel perspective marker of cellular immune system activation, a valid index of stress and systemic inflammation. NLR is a cheap, simple, fast responding and easily available parameter of stress and inflammation with high sensitivity and low specificity. We sought to evaluate NLR and PLR in diabetic ulcers with association to patient and wound-specific factors that may help predict healing of diabetic ulcers. Aims: The association between Neutrophil-Lymphocyte ratio and Platelet-Lymphocyte ratio v/s wound healing in diabetic wounds. Study design: prospective observational study. Place and Duration of Study: Rajarajeswari Medical College, Bangalore; by the Department of General Surgery between 1st of January 2022 till 31st July 2022. Sample: all patients admitted and treated for diabetic ulcers. Methodology: 34 patients chosen in total. Demographic information, baseline wound characteristics, comorbidities, and laboratory data including NPR and PLR were correlated with ulcer healing and progression to healing ulcer or progressing ulcer (requiring further amputation) based on clinical description or daily notes. Results: A total of 34 patients were evaluated. Patients were an average age of 59.3 years. During the follow-up period, 32 ulcers (94.1%) healed and were discharged, while 2 patients died (5.9%).41.1% required amputations. On admission NLR (mean 13.8), PLR (mean 305.9) and on discharge NLR (mean 5.21), PLR (mean 183.7) were calculated which showed a significant decrease (p value of 0.000001) and (p value of 0.0028) respectively, but did not return to normal within 2 month period in all patients. Conclusion: Thus, decreasing or improving NLR and PLR ratios rather than return to normal ratio can be considered as a sign of improving patient condition, while an increasing NLR has shown to be associated with bad prognosis.***

Keywords: Trend, Neutrophil-Lymphocyte ratio, Platelet-Lymphocyte ratio, Diabetic ulcer, Prognostic Marker, healing indicator

1. Introduction

Diabetic foot ulcer is a common and debilitating complication of diabetes mellitus and is the main cause of lower extremity amputations in the diabetic population [1–3].

A challenge with regard to **scoring, prediction of outcome** and **planning of appropriate treatment** plan remains to this day.
Predicting wound healing outcome can lead to better intervention and lower rates of amputation [4, 5].

Blood neutrophil-to-lymphocyte (N/L) ratio is a simple marker of **subclinical inflammation** that is free and can be easily obtained from the differential WBC count. [9]

The N/L ratio has been used to predict outcomes in patients with cancer [6-8] and peripheral artery disease [7, 8] peptic ulcers and ulcerative colitis [9].

We can obtain information about two different immune pathways from the N/L ratio. Firstabout the neutrophils that are responsible for lasting inflammation and the second about the lymphocytes that demonstrate the regulatory pathway [10, 11].

We sought to evaluate DU patients and calculate NLR and PLR, its association to patient and wound-specific factors, thus it may help predict healing of diabetic ulcers

2. Methodology

Aims and Objectives: The association between neutrophil-lymphocyte ratio and platelet-lymphocyte ratio v/s wound healing in diabetic wounds.

Study Design: Retrospective study

Study Period: 6 months (1st of January 2022 till 31st July 2022.)

Study Centre: Department of General Surgery, Rajarajeswari Medical College and Hospitals.

Source of Data: All Diabetic ulcer patients treated by dept of General Surgery of Rajarajeswari Medical College.

Sample Size: 34 patients chosen in total.

Inclusion Criteria:

- All patients diagnosed with Diabetic ulcers of lower limb and admitted for same and underwent debridement's +/- Amputations

- Age 18-80yrs

Exclusion Criteria:

- Patients with immunocompromised illness (HIV, Steroid use)
- Patients with incomplete or missing medical records.
- Patients discharged within 20 days of starting treatment or surgery.
- Patients who were admitted for Plastic surgical procedure/ Secondary closures.

Method

The following information was obtained via case sheets, charts and computer drives. Data was then tabulated and analyzed.

1) **Demographic information**, baseline **wound characteristics** at time of admission and discharge **comorbidities** and Hb_{A1C}
2) **Laboratory data** including Differential leucocyte count (**NLR and PLR** were calculated from this data) at admission and at time of discharge or at 2 months (which ever came 1st)
3) **Final outcome** of patient at the time of discharge was also noted
4) Findings were correlated with ulcer healing and progression to healing ulcer or progressing ulcer (requiring further amputation)

2.1 Statistics

Numerical data were summarized as **mean and range of data**, and Categoric and continuous variable were compared using χ^2 **and independent-sample two-tailed *t*-test**, respectively.

3. Results and Discussion

82 patients were treated in our department, with in the above study period, of which 48 patients were excluded due to presence of exclusion criteria. Thus 34 patients were enrolled in this study.

Of the Patients enrolled,

- An average age of 59.3 years
- Males being 70.6%
- Foot ulcers were commonest, accounting for 85% of all patients suffering from it, followed by ankle and leg ulcers.
- Grade 2 ulcers was commonest, accounting for 35% of all patients presenting with at time of admission followed by grade 5 ulcers in 29% of patients.
- Of all the patients enrolled, 41% had Peripheral vascular disease (diagnosed by arterial or venous doppler or being treated for same or any previous records of it)

Demographic Data

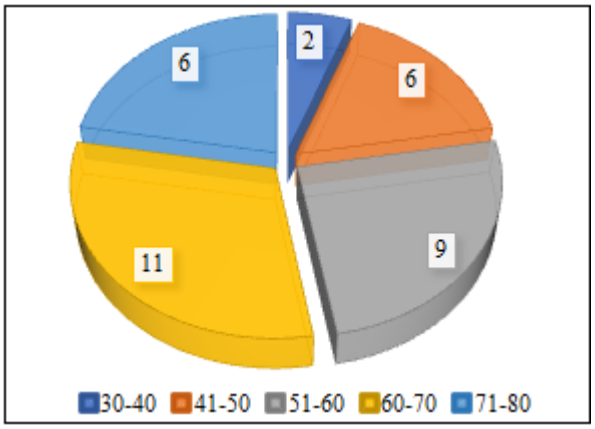

Figure 1: Age of Study Population

The age incidence in this study group ranged from 30-80 years. Most of the patients were in the 60-70 yrs. of age, followed by 51-60yrs of age. Thus 51-70 yrs. represent 55% of affected population.

Table 1: Age of Study Population v/s NLR & PLR (at admission and at discharge)

	NLR			PLR		
	<51	51-70	>70	<51	51-70	>70
PRE-OP	10.7	14.36	16	264	277	454.7
At Discharge	7.5	4.6	4.1	228	171	165

In our study, we found a visible decrease in NLR and PLR ratios **(average)** between at time of admission and discharge, and the change was more prominent in patients belonging to 51-70 yrs. and 70-80 years of age group.

- **Co-morbidities in study population**

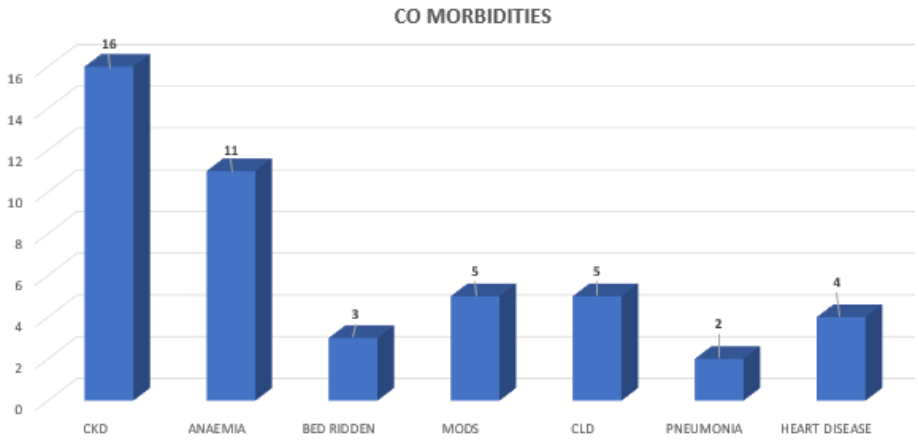

Figure 2: Co-morbidities in study population

In our study, we found Chronic Kidney Disease or renal failure to be the most common co-morbidity presenting with 16 out of 34 patients or in 47% of all patients, followed by anaemia, which was seen in 11 out of 34 patients or 32% of all patients.

Table 2: Age of Study Population v/s NLR & PLR (at admission and at discharge)

		CKD	Anaemia	Bed Ridden	MODS	CLD	PNEUM-ONIA	Heart Disease
PRE-OP	NLR	14.5	18.9	11.7	20.18	16.54	35.4	18
(average)	PLR	192.1	390	367	304	538	197	623.8
Discharge	NLR	5.4	5.2	3.7	6.18	4.4	1.6	5.7
(average)	PLR	194	150	242.8	113	145	52.9	186.3

In our study when NLR and PLR ratios between at time of admission and discharge where analyzed, it showed a decrease in value, but NLR remained higher than normal in patients diagnosed with multi-organ dysfunction, indicating an association between NLR and Multi-organ Injury and PLR remained above normal in bed ridden patients, indicating an association between PLR and chronic heart disease.

- **Outcome of ulcer and patients:**

During the follow-up period, 57.1%of all patients required amputations, 32 patients (94.1%) healed and where discharged, while 2 patients died (5.9%).

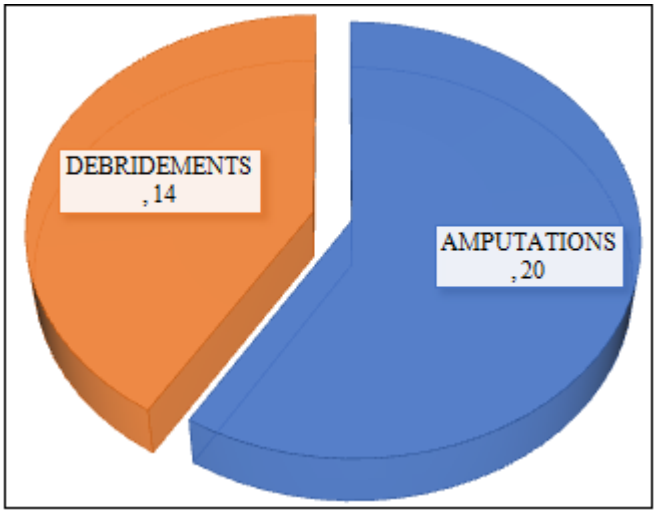

Figure 3: Outcome of ulcer

In our study, we found 20 (57.1%) patients underwent debridement + amputations (minor [rays, forefoot, disarticulations], or major [below or above knee amputations]) which accounts for 58% of our study populations. Rest of patients need only debridement and the wound healed well.

Table 3: Outcome of ulcer v/s NLR & PLR (at admission and at discharge)

	NLR (average)		PLR (average)	
	Debridement	Amputation	Debridement	Amputation
Pre-Op	15.8	12.4	336	284.7
At Discharge	3.7	6.3	145	209.1

In our study when NLR and PLR ratios between at time of admission and discharge were analyzed for patients who underwent debridement and amputations and it showed a decrease in value, but NLR and PLR came within normal range for patients who underwent only debridement showing improvement in patient general condition after surgery.

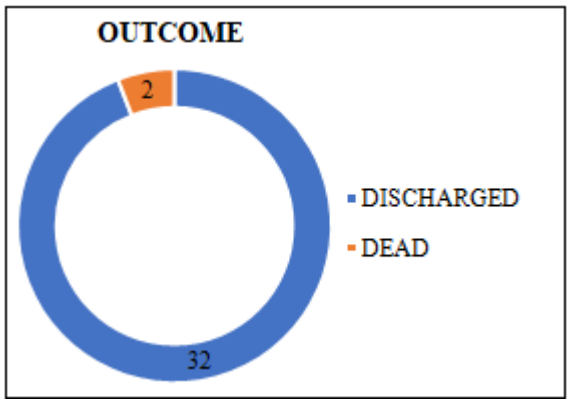

Figure 4: Outcome of ulcer

In our study, we found 20 patients underwent debridement + amputations (minor [rays, forefoot, disarticulations], or major [below or above knee amputations]) which accounts for 58% of our study populations. Rest of patients need only debridement and the wound healed well.

Table 4: Outcome of patient v/s NLR & PLR (at admission and at discharge)

	NLR (average)		PLR (average)	
	Discharged	Dead	Discharged	Dead
Pre-Op	14.2	6	307	278
At Discharge	4.8	11.35	187.2	128.3

In our study when NLR and PLR ratios between at time of admission and discharge where analyzed, it showed a decrease in value, in patients in whom ulcers healed well and were discharged with healed ulcers or healing ulcers for regular dressing or were planned for secondary closure of wounds. However, when NLR was analyzed of patients who succumbed to various organ failures, we noticed an increase in NLR when compared to on admission and this finding was not noted with PLR ratio indicating an association between NLR and bad outcome.

- NLR and PLR v/s WBC Counts

Table 5: WBC v/s NLR v/s PLR (at admission and at discharge)

	WBC		NLR		PLR	
	Range	Average	Range	Average	Range	Average
PRE-OP	3.9-39.4	19.4	6-35.4	13.8	65.2-980	305.9
At Discharge	6.5-22.2	11.3	1.6-19.8	5.2	42.2-460	183.7

In our study when NLR and PLR ratios between at time of admission and discharge where analyzed, it showed a

decrease in value, in patients in whom ulcers healed well and were discharged with healed ulcers or healing ulcers for regular dressing or were planned for secondary closure of wounds. However, when NLR was analyzed of patients who succumbed to various organ failures, we noticed an increase in NLR when compared to on admission and this finding was not noted with PLR ratio indicating an association between NLR and bad outcome.

A) Neutrophil-lymphocyte ratio on admission (mean 13.8) and on discharge (mean 5.21) where calculated which showed a significant decrease (p value of 0.000001) but did not return to normal in 4 the patients
B) Platelet-lymphocyte ratio on admission (mean 305.9) and on discharge (mean 183.7) where calculated which showed a significant decrease (p value of 0.0028) but did not return to normal in 11 the patients
C) Out of all 34 patients,
   - 2 patients succumbed to organ failure, NLR was able to predict it with an increasing NLR
   - 7 patients had chronic ulcers (not healed after 2 months) patients had raised PLR (above normal) at the end of 2 months.

3.1 Cross References

Nasibeh Vatankhah in his study in 2017, studied 120 ulcers until they completely healed and found

- Mean age was **59.4 yrs., 66%** were males**,**
- **48**% healed without amputations and rest needed some or other form of amputation**.**
- Mean NLR was 3.70 ± 1.75, 6.97 ± 6.82, 8.72 ± 5.97, and 8.46 ± 8.94 in complete healing, minor amputation, major amputation, and chronic wounds, respectively (P =.00) [11]

3.1.1 Limitation of Study

- Retrospective Study
- Small Sample Size
- Small Sub Study Groups
- Trends over long periods are needed, thus not preferred in emergencies.
- Variable NLR and PLR normal ranges in different populations and age groups.

4. Conclusion

NLR is cost effective and easily available parameter of stress and inflammation with high sensitivity and low specificity. And it has shown to be dynamic with patients' general condition, thus giving hint on patient's systemic immune status. An improving NLR and PLR ratios rather than return to normal ratio can be considered as a sign of improving patient condition. An increasing NLR has shown to be associated with higher risk of mortality and PLR higher than normal range was associated with higher risk of chronic ulcers or morbidity.

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At last, I would like to thank god for the strength and mercy bestowed on me for this journey to help heal and care for others and myself, and I pray for more as this journey will not end and more work remains.

Competing Interests
Authors have declared that no competing interests exist.

Authors' Contributions
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Consent
Consent was invalidated as these studies were obtained from case files, cloud data base and public records.

Ethical Approval
Ethical approval: Study was approved by the Ethical Committee of the institute

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Definitions, Acronyms, Abbreviations

Neutrophil –lymphocyte ratio (NLR) = differential count of neutrophil / differential count of lymphocytes (Normal range 1- 4)
Platelet – lymphocyteratio (PLR) =Platelet count / differential count of lymphocytes (Normal range 35-200)
WBC Count= total leucocyte count, normal 4-11x10^3 cells per decilitre
CKD = Chronic Kidney Disease or Renal Failure
MODS= Multi Organ Failure
CLD= Chronic Liver Disease
Pre-op= Pre-Operative