Research Article

The role of the platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in the prediction of length and cost of hospital stay in patients with infected diabetic foot ulcers: A retrospective comparative study

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ABSTRACT

Objective: The aim of this study was to determine the role of new inflammatory markers, including the platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR), in the prediction of length and cost of hospital stay in patients with infected diabetic foot ulcers (DFUs).

Methods: A total of 78 patients with DFUs who were admitted to our endocrinology clinic between January 2016 and July 2017 were included. Patients were then divided into three groups according to the Wagner DFU classification system: group 1: 18 patients with grade 2 DFU (11 men, 7 women; mean age = 57.5±7 years); group 2: 44 patients with grade 3 DFU (18 men, 26 women; mean age = 59.7±8.7 years); and group 3: 16 patients with grade 4 DFU (10 men, 6 women; mean age = 59.9±11.6 years). Laboratory findings were retrospectively obtained from hospital records; the PLR and NLR were calculated in all groups. Length and cost of hospital stay were recorded. Hospital costs were estimated in Turkish Lira (TL) based on the evaluation of glucose regulation, wound care, and antibiotic treatment.

Results: The mean NLR was significantly lower in group 1 (2.8±0.9) than in group 2 (6.0±5.2; p=0.017) and group 3 (6.9±5.3; p=0.011). The mean PLR was significantly lower in group 1 (140.8±42.6) than in group 3 (222.1±95.5; p=0.006). The mean length of stay was 7.9±2.7 days in group 1, 15.0±8.9 days in group 2, and 12.5±8.9 days in group 3. The mean cost was 1,310.8±500 TL in group 1, 2,966.9±2105 TL in group 2, and 3,488.1±3603.1 TL in group 3. Length and cost of stay were both significantly lower in group 1 than in groups 2 and 3 (p=0.011 and p=0.002, respectively). Comparative results showed that the length and cost of hospital stay increased with increasing severity of DFUs. Furthermore, correlation analyses demonstrated no correlation of length of stay with PLR and NLR but an obvious correlation between cost of stay and PLR (r=0.412; p<0.001). Additionally, there was no correlation between cost of stay and NLR (r=0.158, p>0.05).

Conclusion: The PLR is inflammatory marker that can be measured by an inexpensive and easily accessible test and can aid in the prediction of length and cost of hospital stay in patients with DFUs.

Level of Evidence: Level III, Therapeutic study

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A diabetic foot ulcer (DFU) is a common complication of diabetes with increased morbidity and mortality (1-3). It is a leading cause of hospitalization among diabetic patients and can lead to infection, gangrene, and amputation, which are responsible for a considerable amount of the huge total costs for diabetes care (4). Many predictors such as clinical scores and laboratory parameters have been studied for estimating the length and cost of stay in hospital, wound healing, and amputation (2, 5-10).

The platelet-to-lymphocyte ratio (PLR) is a new inflammatory marker and independent predictor of major adverse cardiovascular events in different cardiovascular diseases (11). Moreover, the neutrophil-to-lymphocyte ratio (NLR) has been suggested as an indicator of systemic inflammation and a potential marker of inflammation in diabetic micro- and macrovascular complications (12). However, neither the PLR nor the NLR was studied in terms of cost and length of stay in case of DFUs.

We therefore conducted this study to compared the NLR and PLR with conventional inflammatory markers [white blood cell (WBC) count, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP)] in terms of estimating the length and cost of hospital stay in patients with infected DFUs.

Materials and Methods

Data from hospitalized patients with DFUs and infections [diagnosed by the presence of systemic signs of infection, purulent secretions, or at least two local findings of inflammation (e.g., redness, warmth, swelling, pain, and tenderness)] who were admitted to the Endocrinology Clinic between January 1, 2016, and July 1, 2017, were collected for our retrospective comparative study. Written informed consent was obtained from the all participant. Cost was estimated in terms of the evaluation of glucose regulation, ulcer, wound care, and antibiotic treatment. The cost of amputation was not included. Patients with severe hepatic failure, end-stage renal failure, known malignancy, and rheumatological disease and infections other than DFUs were excluded. The details of DFU features and biochemical results were extracted from patient charts and the hospital information system. Data included age, sex, Wagner DFU classification, and cost and length of hospital stay. Biochemical analyses were blood glucose, creatinine, CRP, and hemoglobin (Hgb) levels; glycosylated haemoglobin (A1C); WBC and platelet (PLT) counts; and ESR. The PLR and NLR were calculated from the total blood count. The study protocol conforms to the principles of the Helsinki Declaration and was approved by the local ethical committee.

Patients with Wagner's grade 1 DFUs were not included since they could be treated in the outpatient clinic. We divided our patients into three groups according to the Wagner classification (there was no patient with grade 5 DFUs): group 1: grade 2 DFUs (n=18); group 2: grade 3 DFUs (n=44); and group 3: grade 4 DFUs (n=16). Patients with grade 2 or 3 DFUs who had radiologically detected vascular major occlusion and needed an interventional procedure were excluded.

Statistical analysis

All statically analyses were performed using the Statistical Package for Social Sciences for Windows, version 20.0 (IBM Corp.; Armonk, NY, USA). For continuous variables, the Kolmogorov–Smirnov test was first used to define sample distribution and one-way analysis of variance or the Kruskal–Wallis test was then chosen to compare independent samples. Then, Tukey's or the Mann–Whitney U test was used as a posthoc test. For categorical variables, the Chi-square test was used to detect differences. Pearson's correlation test was used to determine correlations between length and cost of stay and other clinical and laboratory parameters. Data are presented as mean ± standard deviation. A p value < 0.05 was considered statistically significant.

Results

There was no statically significant difference between the groups in terms of mean age; sex; A1c; glucose, creatinine and alanine aminotransferase levels, and PLT count. WBC count was significantly higher in groups 2 and 3 than in group 1 (p=0.008 and p=0.015, respectively). Hgb level was significantly higher in group 1 than in group 3 (p=0.009). CRP levels were significantly higher in groups 2 and 3 than in group 1 (p<0.001 and p=0.009, respectively). ESR was significantly higher in groups 2 and 3 than in group 1 (p<0.001 for all). PLR was significantly lower in group 1 than in group 3 (p=0.006). NLR was significantly lower in group 1 than in groups 2 and 3 (p=0.017 and p=0.011, respectively). Length and cost of stay were significantly lower in group 1 than in groups 2 and 3 (p=0.011 and p=0.002, respectively) (Table 1).

Correlation analyses revealed that length of stay was significantly and positively correlated with PLT count (r=0.328, p=0.003). There was a significant positive correlation between length and cost of stay (r=0.709, p<0.001). In addition, cost of stay was significantly and positively correlated with PLT count (r=0.412, p<0.001), ESR (r=0.284, p=0.012), and PLR (r=0.412, <0.001) and also negatively correlated with Hgb level (r=-0.270, p=0.017) (Table 2).

Discussion

The remarkable findings of the present study were 1) the levels of the conventional markers of acute phase response to inflammation (i.e., WBC, CRP, and ESR) significantly increased with the presence of osteomyelitis and gangrenous lesion, 2) the Hgb levels of patients had decreased in patients with grade 4 DFUs, 3) PLR and NLR tended to be higher in patients with an advanced grade of DFU, 4) both length and cost of stay were positively correlated with PLT count, 5) cost of stay but not length of stay was positively correlated with ESR and PLR, and 6) low Hgb was significantly related to high cost of stay.

High Wagner's grade as well as increased ESR, CRP level, and WBC count are associated with worse clinical outcomes (13). We also found that ESR, CRP level, and WBC count were significantly higher in grade 3 and 4 DFUs than in grade 2 DFUs. Although the Wagner classification does not show the severity of infection, concomitant osteomyelitis and gangrenous lead to acute phase response and increase in inflammatory markers.

> **MAIN POINTS**
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> - Diabetic foot ulcer is a common complication with severe morbidity and mortality.
> - Length and cost of stay in hospital is a main source of diabetes care.
> - Platelet-to-lymphocyte ratio is cheap and accessible inflammatory marker, and may be used for prediction of length and cost of hospital stay in diabetic foot ulcer.

Table 1. Characteristics and laboratory findings in all groups

	Group 1 (n=18)	Group 2 (n=44)	Group 3 (n=16)	p
Age (years)	57.5±7.0	59.7±8.7	59.9±11.6	NS
Gender (male/female)	11/7	18/26	10/6	NS
Glucose (mg/dL)	335.4±166.1	356.6±156.5	285.4±140.0	NS
Creatinine (mg/dL)	0.9±0.3	1.0±0.3	0.9±0.3	NS
ALT (U/L)	17.7±16.3	19.1±16.7	17.1±6.9	NS
A1c (%)	11.2±3.3	11.4±2.3	10.1±2.4	NS
WBC (10⁹/L)	9.9±3.9[a, b]	15.1±7.1	15.7±7.8	0.016
Hgb (g/dL)	12.5±1.7[c]	11.6±1.8	10.9±1.5	0.029
PLT (10⁹/L)	303.6±95.8	379.37±150.1	410.6±127.1	NS
CRP (mg/dL)	4.1±4.5[c, d]	15.8±10.8	12.6±8.8	<0.001
ESR (mm/h)	56.4±17.7[d, e]	83.8±28.7	95.1±26.1	<0.001
PLR	140.8±42.6[f]	185.7±90.2	222.1±95.5	0.02
NLR	2.8±0.9[g, h]	6.0±5.2	6.9±5.3	0.022
Length of stay (days)	7.9±2.7[i]	15.0±8.9	12.5±8.9	0.009
Cost of stay (TL)	1,310.8±500.0[f]	2,966.9±2,105.0	3,488.1±3,603.1	0.02

A1c: glycosylated hemoglobin; ALT: alanine aminotransferase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hgb: hemoglobin; NLR: neutrophil-to-lymphocyte ratio; PLO: platelet-to-lymphocyte ratio; PLT: platelet; WBC: white blood cell

[a]p=0.008 between group 1 and group 2; [b]p=0.015 between group 1 and group 3; [c]p=0.009 between group 1 and group 3; [d]p<0.001 between group 1 and group 2; [e]p<0.001 between group 1 and group 3; [f]p=0.006 between group 1 and group 3; [g]p=0.017 between group 1 and group 2; [h]p=0.011 between group 1 and group 3; [i]p=0.002 between group 1 and group 3

As novel inflammation markers, the PLR and NLR have been investigated in cardiovascular disease, diabetes, and diabetes-associated vascular complication (11, 14-17). Furthermore, both the PLR and NLR were found to be associated with peripheral vascular disease and its severity (18, 19). Vatankhah et al. showed that low NLR was an independent predictor of complete wound healing in DFUs (20). To the best of our knowledge, there is no study that evaluated the role of the PLR in DFUs. We found that the PLR and NLR gradually increased with Wagner's grade. Further clinical studies are needed to evaluate the predictive role of the PLR in wound healing in case of DFUs.

The considerable amount in the total diabetes cost includes DFU management (21). Amputation-if necessary-and indirect costs (losses in productivity, preventive efforts, rehabilitation, and home care) contribute to economic burden as well as the management of DFUs (4). Nearly one-third of the total cost during the treatment of diabetes and its complication has been spent for DFUs; a large amount was for hospital stay (22-24). When infection complicated DFUs, the risk of hospitalization increased 55 times compared to when DFUs were without infection (2). In our study, length and cost of stay gradually increased with Wagner's grade. Similarly, Benotmane et al. showed that high Wagner's grade was associated with increased length and cost of stay (25). In our study, cost and length of stay in group 4 and probably in group 3 may have been much more since we did not

take into account amputation and postamputation duration and costs. There were several studies evaluating the length of stay in diabetic patients (26-28). Kim et al. found that ESR, A1c, body mass index, and major vascular disease were significant factors that affected length of stay in infected DFUs (10). Tabur et al. showed that CRP, WBC, ESR, and increased Wagner's grade can predict length of stay in case of acute DFUs (9). In our study, we found that only PLT count was a positive predictor of length of stay.

Hospitalization requirement increase with the severity of ulcers according to the Wagner classification, resulting in high costs, a finding similar to our results (23). The predictive role of the NLR in terms of the length and cost of stay for acute ischemic stroke has been previously shown (29). However, the predictive role of the PLR and NLR during the course of DFUs is not known. In our study, we found for the first time that the PLR, which can be measured by a cheap and simple test, can predict cost of stay in case of infected DFUs. Although the PLR and NLR were not more sensitive markers than conventional markers, they are calculated from complete blood count.

The most important limitation of our study was the retrospective nature. Additionally, the cost of amputation was not evaluated. Nevertheless, the first-time evaluation of the PLR and NLR in case of DFUs will result in similar and comprehensive studies in the future.

Table 2. Correlation analyses between the length and cost of stay and clinical and biochemical parameters of patients

Length of stay (days)	r	p
Age (years)	0.107	NS
Glucose (mg/dL)	0.068	NS
Creatinine (mg/dL)	0.071	NS
ALT (U/L)	-0.026	NS
A1c (%)	0.009	NS
WBC (10^9/L)	0.202	NS
Hgb (g/dL)	-0.204	NS
PLT (10^9/L)	0.328	0.003
CRP (mg/dL)	0.150	NS
ESR (mm/h)	0.214	NS
PLR	0.071	NS
NLR	0.021	NS
Cost of stay (TL)	0.709	<0.001
Cost of stay (TL)	**r**	**p value**
Age (years)	0.107	NS
Glucose (mg/dL)	-0.002	NS
Creatinine (mg/dL)	-0.038	NS
ALT (U/L)	0.062	NS
A1c (%)	-0.105	NS
WBC (10^9/L)	0.148	NS
Hgb (g/dL)	-0.270	0.017
PLT (10^9/L)	0.395	<0.001
CRP (mg/dL)	0.213	NS
ESR (mm/h)	0.284	0.012
PLR	0.412	<0.001
NLR	0.158	NS
Length of stay (days)	0.709	<0.001

A1c: glycosylated hemoglobin; ALT: alanine aminotransferase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; Hgb: hemoglobin; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; PLT: platelet; WBC: white blood cell

In conclusion, the PLR and NLR can be measured by a cheap and easily accessible test since they are calculated from a routine complete blood count. Furthermore, they are new inflammatory markers and can be a predictor of cost and associated with the grade of ulcers in hospitalized patients with infected DFUs.

Ethics Committee Approval: Ethics committee approval was received for this study from the Local Ethics Committee of Harran University (05.01.2017, 01 session and decision 07).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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References

1. Pickwell K, Siersma V, Kars M, et al. Predictors of lower-extremity amputation in patients with an infected diabetic foot ulcer. Diabetes Care 2015; 38: 852-7. [CrossRef]
2. Lavery LA, Armstrong DG, Wunderlich RP, et al. Risk factors for foot infections in individuals with diabetes. Diabetes Care 2006; 29:1288-93. [CrossRef]
3. Beyaz S, Güler ÜÖ, Bağır GŞ. Factors affecting lifespan following below-knee amputation in diabetic patients. Acta Orthop Traumatol Turc 2017; 51: 393-7. [CrossRef]
4. Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on the management of diabetic foot ulcer. World J Diabetes 2015; 6: 37-53. [CrossRef]
5. Yesil S, Akinci B, Yener S, et al. Predictors of amputation in diabetics with foot ulcer: single center experience in a large Turkish cohort. Hormones (Athens) 2009; 8: 286-95. [CrossRef]
6. Callahan D, Keeley J, Alipour H, et al. Predictors of severity in diabetic foot infections. Ann Vasc Surg 2016; 33: 103-8. [CrossRef]
7. Yusof NM, Rahman JA, Zulkifly AH, et al. Predictors of major lower limb amputation among type II diabetic patients admitted for diabetic foot problems. Singapore Med J 2015; 56: 626-31. [CrossRef]
8. Ignatyeva VI, Severens JL, Ramos IC, Galstyan GR, Avxentyeva MV. Costs of hospital stay in specialized diabetic foot department in Russia. Value Health Reg Issues 2015; 7: 80-6. [CrossRef]
9. Tabur S, Eren MA, Çelik Y, et al. The major predictors of amputation and length of stay in diabetic patients with acute foot ulceration. Wien Klin Wochenschr 2015; 127: 45-50. [CrossRef]
10. Kim TG, Moon SY, Park MS, et al. Factors Affecting Length of Hospital Stay and Mortality in Infected Diabetic Foot Ulcers Undergoing Surgical Drainage without Major Amputation. J Korean Med Sci 2016; 31: 120-4. [CrossRef]
11. Uzun F, Erturk M, Cakmak HA, et al. Usefulness of the platelet-to-lymphocyte ratio in predicting long-term cardiovascular mortality in patients with peripheral arterial occlusive disease. Postepy Kardiol Interwencyjnej 2017; 13: 32-8. [CrossRef]
12. Liu S, Zheng H, Zhu X, et al. Neutrophil-to-lymphocyte ratio is associated with diabetic peripheral neuropathy in type 2 diabetes patients. Diabetes Res Clin Pract 2017; 130: 90-7. [CrossRef]
13. Lipsky BA, Sheehan P, Armstrong DG, Tice AD, Polis AB, Abramson MA. Clinical predictors of treatment failure for diabetic foot infections: data from a prospective trial. Int Wound J 2007; 4: 30-8. [CrossRef]
14. DiGangi C. Neutrophil-lymphocyte ratio: Predicting cardiovascular and renal complications in patients with diabetes. J Am Assoc Nurse Pract 2016; 28: 410-4. [CrossRef]

15. Mertoglu C, Gunay M. Neutrophil-Lymphocyte ratio and Platelet-Lymphocyte ratio as useful predictive markers of prediabetes and diabetes mellitus. Diabetes Metab Syndr 2017; 11: 127-31. [CrossRef]

16. Demirtas L, Degirmenci H, Akbas E, et al. Association of hematological indicies with diabetes, impaired glucose regulation and microvascular complications of diabetes. Int J Clin Exp Med 2015; 8: 11420-7.

17. Akbas EM, Demirtas L, Ozcicek A, et al. Association of epicardial adipose tissue, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio with diabetic nephropathy. Int J Clin Exp Med 2014; 7: 1794-1801.

18. Teperman J, Carruthers D, Guo Y, et al. Relationship between neutrophil-lymphocyte ratio and severity of lower extremity peripheral artery disease. Int J Cardiol 2017; 228: 201-4. [CrossRef]

19. Gary T, Pichler M, Belaj K, et al. Platelet-to-lymphocyte ratio: a novel marker for critical limb ischemia in peripheral arterial occlusive disease patients. PLoS One 2013; 8: e67688. doi: 10.1371/journal.pone.0067688. [CrossRef]

20. Vatankhah N, Jahangiri Y, Landry GJ, et al. Predictive value of neutrophil-to-lymphocyte ratio in diabetic wound healing. J Vasc Surg 2017; 65: 478-83. [CrossRef]

21. Barshes NR, Saedi S, Wrobel J, Kougias P, Kundakcioglu OE, Armstrong DG. A model to estimate cost-savings in diabetic foot ulcer prevention efforts. J Diabetes Complications 2017; 31: 700-7. [CrossRef]

22. Driver VR, Fabbi M, Lavery LA, Gibbons G. The costs of diabetic foot: the economic case for the limb salvage team. J Vasc Surg 2010; 52(3 Suppl): S17-22. [CrossRef]

23. Stockl K, Vanderplas A, Tafesse E, Chang E. Costs of lower-extremity ulcers among patients with diabetes. Diabetes Care 2004; 27: 2129-34. [CrossRef]

24. Oksuz E, Malhan S, Sonmez B, Numanoglu Tekin R. Cost of illness among patients with diabetic foot ulcer in Turkey. World J Diabetes 2016; 7: 462-9. [CrossRef]

25. Benotmane A, Mohammedi F, Ayad F, Kadi K, Medjbeur S, Azzouz A. Management of diabetic foot lesions in hospital: costs and benefits. Diabetes Metab 2001; 27: 688-94.

26. Currie CJ, Morgan CL, Peters JR. The epidemiology and cost of inpatient care for peripheral vascular disease, infection, neuropathy, and ulceration in diabetes. Diabetes Care 1998; 21: 42-8. [CrossRef]

27. Hicks CW, Selvarajah S, Mathioudakis N, et al. Burden of Infected Diabetic Foot Ulcers on Hospital Admissions and Costs. Ann Vasc Surg 2016; 33: 149-58. [CrossRef]

28. Kubo T, Fujino Y, Murata A, et al. Prevalence of type 2 diabetes among acute inpatients and its impact on length of hospital stay in Japan. Intern Med 2011; 50: 405-11. [CrossRef]

29. Zhao L, Dai Q, Chen X, et al. Neutrophil-to-lymphocyte ratio predicts length of stay and acute hospital cost in patients with acute ischemic stroke. J Stroke Cerebrovasc Dis 2016; 25: 739-44. [CrossRef]