

From the Society for Vascular Surgery

Predictive value of neutrophil-to-lymphocyte ratio in diabetic wound healing

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ABSTRACT

Objective: The neutrophil-to-lymphocyte ratio (NLR) has been used as a surrogate marker of systemic inflammation. We sought to investigate the association between NLR and wound healing in diabetic wounds.

Methods: The outcomes of 120 diabetic foot ulcers in 101 patients referred from August 2011 to December 2014 were examined retrospectively. Demographic, patient-specific, and wound-specific variables as well as NLR at baseline visit were assessed. Outcomes were classified as ulcer healing, minor amputation, major amputation, and chronic ulcer.

Results: The subjects' mean age was 59.4 ± 13.0 years, and 67 (66%) were male. Final outcome was complete healing in 24 ulcers (20%), minor amputation in 58 (48%) and major amputation in 16 (13%), and 22 chronic ulcers (18%) at the last follow-up (median follow-up time, 6.8 months). In multivariate analysis, higher NLR (odds ratio, 13.61; $P = .01$) was associated with higher odds of nonhealing.

Conclusions: NLR can predict odds of complete healing in diabetic foot ulcers independent of wound infection and other factors. (*J Vasc Surg* 2016;■:1-6.)

Diabetic foot ulcer is a debilitating complication of diabetes mellitus and is the main cause of lower extremity amputations in the diabetic population.¹⁻³ Predicting wound healing outcome can lead to better intervention and lower rates of amputation.^{4,5} Several tests have been shown to predict wound healing in the diabetic foot.⁵ The neutrophil-to-lymphocyte ratio (NLR) has recently been shown to predict overall and disease-specific mortality and chemotherapy response in cancer patients.⁶⁻⁸ NLR is also shown to be associated with complexity of peripheral arterial disease,⁹ systemic endothelial dysfunction,¹⁰ and cardiovascular diseases.¹¹ No study has investigated the predicting value of NLR for wound healing outcome in diabetic foot ulcers. The objective of this study was to evaluate the association between NLR and treatment outcomes in diabetic foot ulcers.

METHODS

Patients. The protocol was approved by the Institutional Review Board of the Oregon Health & Science University, and informed consent was waived. Subjects referred to the vascular surgery clinic with diabetic foot ulcer from August 2011 to December 2014 were included in the study. After exclusion of those with missing data on their baseline neutrophil or lymphocyte count, 120 ulcers in 101 patients were studied. The ulcers were observed until complete healing, amputation (minor or major), or last clinical follow-up. The last follow-up date in chronic wounds was February 2016.

Definitions. Outcome of ulcers was classified as complete wound healing, minor amputation, major amputation, and chronic wounds. Ulcers that did not reach complete healing or amputation during the follow-up period were considered chronic wounds; ulcers that reached complete healing without amputation were considered complete healing. For analysis purposes, any amputation or chronic wounds were considered nonhealing ulcers. Amputations below the ankle were classified as minor amputations, and amputations higher than this level were defined as major amputations.

Wound infection was defined on the basis of the Wound, Ischemia, and foot Infection (WIFI) criteria or a report of a positive result of wound tissue culture.¹²

Peripheral arterial disease was determined by meeting one of the following criteria:

1. Ankle-brachial index <0.92
2. Toe-brachial index <0.6
3. Undergoing revascularization as part of current ulcer treatment

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N.V. is supported by NIH Postdoctoral Fellowship Award T32-HL094294.

Author conflict of interest: none.

Presented at the poster session at the 2016 Vascular Annual Meeting of the Society for Vascular Surgery, National Harbor, Md, June 8-11, 2016.

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The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

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<http://dx.doi.org/10.1016/j.jvs.2016.08.108>

Table I. Baseline characteristics of the study population and comparison with excluded subjects

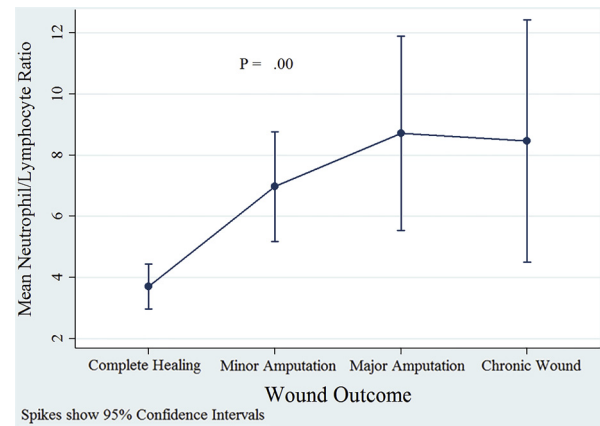
	Study population ^a	Excluded population ^a	P value ^b
Patients	(n = 101)	(n = 38)	
Age, years	59.4 ± 13.0	64.0 ± 12.4	.06
Gender			
Female	34 (34)	14 (37)	.72
Male	67 (66)	24 (63)	
BMI, kg/m ²	33.3 ± 10.3	31.0 ± 5.8	.10
Type of DM			
Type 1	18 (18)	6 (16)	.78
Type 2	83 (82)	32 (84)	
Smoking status			
Never smoked	37 (37)	12 (32)	.75
Past smoker	38 (38)	17 (45)	
Current smoker	25 (25)	9 (23)	
Ulcers	(n = 120)	(n = 44)	
Wound age, days	103.8 ± 213.2	100.4 ± 157.4	.91
Affected side			
Right	58 (48)	23 (52)	.65
Left	62 (52)	21 (48)	
Infection			
Yes	70 (58)	17 (39)	.02
No	50 (42)	27 (61)	
Peripheral arterial disease ^c			
Yes	62 (52)	26 (59)	.40
No	58 (48)	18 (41)	
Vascular intervention			
Yes	32 (27)	11 (25)	.83
No	88 (73)	33 (75)	
NLR	6.82 ± 6.66		
Blood glucose on referral, mg/dL	209.7 ± 124.5	162.1 ± 83.6	.03
Systolic blood pressure on referral, mm Hg	133.3 ± 23.9	132.1 ± 18.6	.77
Outcome			
Complete healing	24 (20)	12 (27)	.55
Minor amputation	58 (48)	20 (45)	
Major amputation	16 (14)	3 (7)	
Chronic wound	22 (18)	9 (21)	
Time to heal, months	7.3 ± 6.2	5.9 ± 4.3	.48
Chronic wound follow-up time, months	12.3 ± 13.6	7.0 ± 5.2	.13

BMI, Body mass index; DM, diabetes mellitus; NLR, neutrophil-to-lymphocyte ratio.

^aNumerical data are summarized as mean ± standard deviation, and categorical measures are shown as frequency (percentage).

^bNumerical measures are compared with independent samples *t*-test, and frequencies are compared using χ^2 test.

^cDefined as ankle-brachial index <0.92 or toe-brachial index <0.6 or vascular intervention for current ulcer treatment.

**Fig 1.** A comparison of mean neutrophil-to-lymphocyte ratio (NLR) in different wound outcome groups; the *P* value shows the result of *W* test.

Time to heal was measured from the baseline evaluation on referral.

Statistical analysis. Numerical data were summarized as mean ± standard deviation, and categorical variables were summarized as frequency (percentage). Independent samples *t*-test and one-way analysis of variance were used to compare mean values between two and more than two groups, respectively. In cases of significantly different variances between groups (determined by the Bartlett test for equal variances), the analysis of variance test was replaced with a *W* test. To evaluate univariate and multivariate associations between NLR and wound healing, binomial generalized estimating equations logit models were constructed with healed/not healed wounds as outcome variable. There were multiple observations in some cases, so we set the patients' unique id as the identifier cluster variable. Then, standardized values of NLR and other numerical variables were entered in generalized estimating equation models to cope with the inherent patient effect on the results. The multivariate model was adjusted for patients' age, gender, body mass index, smoking status, type of diabetes, systolic blood pressure, serum glucose levels, wound age, wound infection, affected limb, and presence of peripheral arterial disease on referral. We determined the optimal cutoff value for NLR for predicting ulcer outcome with maximum sensitivity and specificity using a nonparametric receiver operating characteristic curve by Youden method. All analyses were done using Stata InterCooled 14.1 for Windows (StataCorp LP, College Station, Tex). *P* value < .05 was considered significant.

RESULTS

Table I shows the baseline characteristics of the study population and a comparison with excluded subjects.

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