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ORIGINAL ARTICLE

Presence of Sensory Neuropathy Modifies the Predictive Value of Inflammatory Biomarkers for Osteomyelitis in Diabetic and Nondiabetic Patients with Foot Infections

Easton Ryan, BS*
Junho Ahn, MD†
Dane K. Wukich, MD†
Javier La Fontaine, DPM, MS*
P. Andrew Crisologo, DPM‡
Matthew Malone, PhD§
Orhan K. Oz, MD, PhD||
Lawrence A. Lavery, DPM, MPH*

*Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, Texas
†Department of Orthopedic Surgery, University of Texas Southwestern Medical Center, Dallas, Texas
‡Department of Vascular Surgery, University of Cincinnati, Cincinnati, OH
§South West Sydney Limb Preservation and Wound Research Academic Unit, South Western Sydney LHD, Sydney, Australia
||Department of Radiology, University of Texas Southwestern medical center, Dallas, Texas

Corresponding Author: Easton Ryan, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, Texas, USA, Office: +12146489114. Fax: +12146482550. E-mail: Easton.ryan@utsouthwestern.edu

Objective: To investigate the predictive value of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in persons with and without diabetes with osteomyelitis (OM).

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Methods: We evaluated 455 patients in a retrospective cohort study of patients admitted to the hospital with diabetic foot osteomyelitis [OM] (n=177), diabetic foot soft tissue infections (STIs) (n=176), non-diabetic OM (n=51) and non-diabetic STIs (n=51). Infection diagnosis was determined through bone culture, histopathology for OM, and/or imaging (MRI/SPECT CT) for STI. The optimal cutoffs of ESR and CRP in predicting OM were determined by receiver operating characteristic (ROC) analysis. Sensitivity and specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR–) were determined through contingency tables.

Results: In persons without diabetes with STI and OM the mean ESR and CRP difference was 10.0 mm/hr. and 2.6 mg/dL. In contrast persons with diabetes had higher levels of each, 24.8 mm/hr. and 6.8 mg/dL, respectively. As a result, ESR and CRP predicted OM better in patients with DM. However, when patients were stratified by neuropathy status, ESR remained predictive of OM in diabetic patients with neuropathy (75% sensitivity, 58% specificity) but not in diabetic patients without neuropathy (50% sensitivity, 44% specificity). CRP remained predictive irrespective of neuropathy status. A similar trend was observed in patients without diabetes.

Conclusions: Previous studies have reported that ESR and CRP are predictive of osteomyelitis. However, the current study suggests that neuropathy influences the predictive value of inflammatory biomarkers. The underlying mechanisms requires further study.

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Osteomyelitis (OM) of the foot is challenging and expensive for clinicians to diagnose and treat. The diagnosis of OM incorporates various diagnostic tests including physical examination [1,2], radiographs [3], Magnetic Resonance Imaging (MRI) [4], bone scans, SPECT/CT after injection of radiolabeled white blood cell scans (WBC-SPECT/CT) [5,6], histopathology and bone culture [7,8]. Erythrocyte sedimentation rate (ESR) and C- reactive protein (CRP) are perhaps the most commonly used inflammatory biomarkers in diagnostic algorithms for osteomyelitis [9]. These simple laboratory tests are readily available, relatively inexpensive and have well established diagnostic utility in diagnosing vertebral osteomyelitis, long bone infections and periprosthetic joint infections. However, the literature reports variability in the threshold values based on the anatomic site of infection and the mechanism of infection [10-13]. The cut-off values for CRP and ESR to diagnose diabetic foot osteomyelitis are 2-5 times higher than reports of osteomyelitis at other anatomic site [9].

The existing literature for osteomyelitis of the foot is limited because of small sample sizes, inconsistent reference standards to diagnose osteomyelitis, and the exclusive evaluation of people with diabetes. In addition, ESR is usually the only biomarker evaluated, so there is little evidence to support the use of CRP to diagnose OM [9]. The vast majority of infected foot ulcers occur in people with diabetes. In fact, there are few published reports of foot infections in people without diabetes [14-17]. Therefore, there is little evidence concerning the diagnostic value of commonly used tests to evaluate osteomyelitis in people without

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diabetes [14]. Healthcare providers tend to extrapolate the medical evidence for diabetic foot infections to people without diabetes. Conversely, it is not uncommon for providers to apply evidence from other sites (spine, pelvis and long bones) to the foot. The goal of this study was to evaluate the sensitivity, specificity, positive predictive value (PPV), negative predictive values (NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR–) of ESR and CRP in patients with and without DM to predict pedal osteomyelitis.

Methods

After IRB approval, inpatient medical records were reviewed, identifying 455 adult patients who had admitted to the hospital with a foot infection. The records reflected patients admitted from June 12, 2009 through February 21, 2017. We separated the patients into four groups with foot infection; diabetic patients with OM, diabetic patients with STIs, non-diabetic patients with OM, and non-diabetic patients with STIs. The diagnosis of OM was based on positive bacterial cultures from bone specimens and/or histological changes consistent with osteomyelitis. Patients with STIs by definition had a negative bone culture and histology, or a MRI or SPECT CT study that was negative for osteomyelitis. Other inclusion criteria were age between 18 and 89 years old, and baseline ESR and CRP measured within 72 hours of admission. We excluded patients with comorbidities that could affect baseline ESR and CRP levels (i.e. autoimmune disease and other sites of infection like endocarditis were excluded).

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A detailed medical review also collected data regarding demographics, medical history, results of other serological tests, imaging, and cultures. Diagnosis of diabetes mellitus was based on criteria from the American Diabetes Association. We defined sensory neuropathy as abnormal vibration sensation, abnormal sensation with 10 gram Semmes-Weinstein monofilament, and/or absent Achilles deep tendon reflexes [18,19]. We evaluated the values of ESR and CRP from the medical charts, analyzed by the hospital biochemistry laboratory

All continuous variables were tested for normality using Shapiro-Wilk analysis. Descriptive statistical analyses were utilized to determine frequencies of categorical variables and median values of continuous variables with 25th to 75th interquartile range (IQR) (Table 1). Continuous variables between STI and DFO study groups were analyzed using either Student's t test (if normally distributed) or Mann-Whitney U test (for non-parametric data) and categorical variables were analyzed using Pearson's chi-square tests or Fisher's exact test when appropriate. Contingency tables were used to calculate descriptive epidemiologic measures, and area under the receiver operating characteristic (ROC) curve for osteomyelitis were calculated for both ESR and CRP. Various cut off levels of ESR and CRP were tested to maximize sensitivity and specificity (Table 2). Optimal threshold values of ESR and CRP were identified by the highest combined rate of sensitivity and specificity results for each cutoff point (Youden's J statistic) [12]. Potential interaction effects between patient factors such as comorbidities were determined through interaction plots to evaluate for effect modification when correlating factors with ESR and CRP. An alpha value

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of 0.05 was used in all statistical analysis to denote significance. All statistical analyses were performed using R version 3.3.1 (Vienna, Austria).

Results

The median age of patients was 54 years (interquartile range=45-61, Table1). Seventy-five percent of patients were male. No differences in age or sex were observed between DM and non-DM patients. However, patients with DM had significantly greater body-mass index (BMI), history of foot ulceration, ankle-brachial index (ABI), white blood cell count (WBC), ESR, CRP levels and presence of peripheral artery disease (PAD), neuropathy, and retinopathy. Furthermore, patients with DM had lower glomerular filtration rates (GFR), serum albumin levels and hemoglobin levels. Next we compared the mean differences of ESR and CRP. The mean difference was the difference between the averages. We subtracted the ESR and CRP averages of DM OM group from DM STI group which resulted in differences of 10.0 mm/h and 2.6 mg/dL respectively. However, persons with diabetes with STIs and OM had greater mean differences in ESR and CRP of 24.8 mm/hr. and 6.8 mg/dL, respectively. In addition, ESR and CRP tended to predict OM versus STI with greater sensitivity and specificity in patients with DM than those without DM (Table2). However, when patients were stratified by presence or absence of neuropathy, ESR remained predictive of OM in diabetic patients with neuropathy (OR 4.16, 95% CI 2.58-6.72) whereas ESR was not significantly predictive in diabetic patients without neuropathy (OR 0.78, 95% CI 0.20-3.01, Table 2). This relationship was not observed with CRP values, as CRP

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remained predictive regardless of neuropathic status. When patients without diabetes were stratified by presence or absence of neuropathy, a similar change was seen with ESR becoming more predictive of OM in neuropathic patients (OR 5.91, 95% CI 1.70-20.5) and not significantly predictive in non-neuropathic patients (OR 3.43, 95% CI 0.94-12.5). None of the patient factors demonstrated significant interaction. As such, it is unlikely that any factors modified the effect of co-morbidities on ESR and CRP.

Discussion

ESR and CRP are inflammatory biomarkers that are inexpensive and readily available in clinical practice. The cut-off values used to define osteomyelitis are much higher in people with diabetes than the cut-off values used to predict osteomyelitis at other anatomic [10-13,20-23]. This is the first study to evaluate the differences in ESR and CRP and evaluate the role of diabetes, neuropathy, PAD, retinopathy, and chronic kidney disease. In contrast, these co-morbidities are often not documented in other studies of soft tissue and bone infections at other anatomic sites and from other mechanisms of infection.

Diabetic foot infections were associated with significantly higher inflammatory biomarker levels than non-diabetic foot infections. In patients with foot infections, both patients with and without DM had significantly higher ESR in patients with OM (Figure 1a); however, CRP was only significantly different in patients with DM (Figure 1b). To determine which factors were responsible for the apparent effect in diabetic patients, common diabetes-

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associated comorbidities of PAD, retinopathy and neuropathy were independently investigated. Interestingly, we found that in patients without neuropathy, the ESR could not predict OM in patients with and without DM. However, in diabetic patients without neuropathy, CRP remained a significant predictor of OM with a sensitivity of 56% and a specificity of 88%.

Elevations in CRP and ESR correlate with several clinical conditions (i.e. diabetes, neuropathy, vascular complication, obesity and inflammatory arthritis) and have been used as markers of morbidity and mortality [24-28]. CRP has been used as a diagnostic biomarker for sensory neuropathy in people without diabetes [29]. The patient profile for many of the patients that are admitted to hospital with foot infections include many of the co-morbidities associated with an elevation in ESR and CRP. For instance, in this study patients with diabetes had higher BMI, and a higher prevalence of sensory neuropathy PAD, retinopathy, and CKD (Table 1). Baseline CRP and ESR values may be elevated before soft tissue or bone infection develop.

Although peripheral sensory neuropathy significantly altered the predictive value of ESR for OM of the foot, the presence or absence of neuropathy did not sufficiently explain the difference of ESR and CRP between patients with and without DM. As a result, further study is needed to explain the difference of inflammatory biomarkers in patients with DM. Furthermore, the presence of multiple comorbidities may affect ESR and CRP, but we did

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not observe any interaction effects using linear modeling between neuropathy and the other co-morbidities based on diabetes status. Therefore, the effect of neuropathy on ESR was not modified by other patient comorbidities.

The authors acknowledge the limitations of this study. This is a retrospective study, and therefore some of the disease processes may have variable operational definitions, inconsistent testing and documentation. One of the strengths of the current data set is that it was uniformly obtained by faculty and fellows working on the Diabetic Limb Salvage Service, who follow an algorithmic approach to perform and document clinical examination in patients with foot infections. Examination for sensory neuropathy is one of the standard aspects of our evaluation, and this is rarely reported by advanced practice providers, primary care physicians and surgeons not specialized in diabetic foot disease. Another limitation of this study is that we did not evaluate the severity of peripheral sensory neuropathy, however, our finding should stimulate further study.

This study has several advantages compared to other studies that evaluate biomarkers to predict osteomyelitis. This is a large study compared to previous reports in diabetic foot infections [9]. We compared ESR and CRP in patients with and without diabetes and evaluated the effect of common comorbidities. We used bone biopsy as the reference standard to define osteomyelitis. Most other studies use a combination of clinical examination, radiograph changes and probe to bone, MRI or SPECT CT. We used imaging that has low rates of false negatives and low negative likelihood ratios to identify patients

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that did not have osteomyelitis when bone cultures were not indicated or available [4]. In addition, we evaluated both ESR and CRP. Most studies that evaluate foot infections only use ESR [9].

In conclusion, our data supports assessing DM status and peripheral sensory neuropathy in patients presenting with infected foot ulcers as an important initial step when evaluating OM. Further study is needed to elucidate the association between neuropathy and inflammatory biomarkers, and to evaluate the potential impact of neuropathy on the utility of ESR and CRP in the diagnostic algorithm of foot OM.

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Conflict of Interest: Dane K. Wukich is in a consulting and advisory role for Orthofix and Arthrex; Lawrence A. Lavery has consulting agreements with EO2 Concepts, Cardinal Health, Bayer, Medline Industries, Boehringer Ingelheim, and Medimmune.

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Table 1. Patient characteristics and laboratory values grouped by presence or absence of diabetes as well as presence of soft-tissue infection or osteomyelitis.

	Diabetes			No Diabetes			
	Overall	STI	OM	Overall	STI	OM	
Parameter	N = 353	N = 176	N = 177	N = 102	N = 51	N = 51	**P-value[a]**
Patient Factors							
Age, median, years	54 (46-61)	54 (45-60)	54 (47-62)	53.5 (39-61)	52 (40-61)	55 (38-62)	
Male gender, N (%)	262 (74.5)	130 (73.9)	133 (75.6)	76 (74.5)	39 (76.5)	37 (72.5)	
Diabetes Mellitus							
Type 2, N (%)	339 (96.0)	170 (96.6)	169 (95.5)	-	-	-	
Comorbidities, N (%)							
Cardiac disease	212 (60.1)	152 (86.4)	60 (33.9)	48 (47.1)	22 (43.1)	26 (51.0)	**1, 2**
Retinopathy	100 (28.4)	40 (22.7)	60 (34.1)	0 (0.0)	0 (0.0)	0 (0.0)	-
Neuropathy	319 (90.4)	160 (90.9)	159 (89.8)	55 (53.9)	20 (39.2)	35 (68.6)	**1, 2, 3, 4**
Previous ulcer	228 (64.6)	110 (62.5)	118 (66.7)	37 (36.3)	16 (31.4)	21 (41.2)	**1, 2, 3, 4**
Amputation[b]	134 (38.0)	70 (39.8)	64 (36.2)	11 (10.8)	2 (3.92)	9 (17.6)	**1, 2, 4**
PAD	250 (70.8)	127 (72.2)	123 (69.5)	40 (39.2)	18 (35.3)	22 (43.1)	**1, 2, 3, 4**
Laboratory values[c]							
HbA1c	8.8 (7.1-11)	8.7 (7-10.7)	8.9 (7.1-11)	-	-	-	
GFR[d]	60 (42-60)	60 (41-60)	60 (42-60)	60 (60-60)	60 (60-60)	60 (60-60)	**1, 2, 3, 4**
CKD 5: < 15	42 (11.9)	21 (11.9)	21 (11.9)	2 (1.96)	1 (1.96)	1 (1.96)	
CKD 1-4: 15-60	88 (25.0)	43 (24.4)	45 (25.6)	6 (5.88)	1 (1.96)	5 (9.8)	**1, 4**
No CKD: ≥ 60	221 (62.8)	111 (63.1)	110 (62.5)	94 (92.2)	49 (96.1)	45 (88.2)	**1, 2, 3, 4**
Hemoglobin	11.4 (9.9-13)	11.6 (10-13)	11.1 (10-13)	12.7 (12-14)	13.3 (12-14)	12.3 (12-14)	**1, 3, 4**
Serum albumin	3.4 (2.9-3.8)	3.4 (3.1-3.8)	3.4 (2.9-3.1)	3.7 (3.4-4.0)	3.8 (3.4-4.3)	3.6 (3.4-3.9)	**1, 3, 4**
ABI[e]	1.13 (1-1.3)	1.13 (1-1.2)	1.14 (1-1.3)	1.18 (.8-1.3)	1.03 (.5-1.3)	1.18 (1-1.3)	**4**
BMI	30.7 (26-36)	30.7 (26-37)	30.2 (26-36)	26.2 (23-32)	26 (24-32)	26.5 (23-31)	**1, 2, 3, 4**
CRP[f]	4.4 (1.3-11)	2.6 (0.8-7.2)	8.3 (2.6-17)	2.05 (1-6)	1.8 (1-5)	2.3 (1-7.3)	**3, 4**
ESR[g]	68 (45-105)	55 (32-84)	85 (56-119)	33.5 (18-53)	30 (17-44)	42 (24-61)	**1, 2, 3, 4**

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DM = Diabetes Mellitus; IQR = Interquartile Range (25th to 75th percentile); GFR = Glomerular Filtration Rate; ABI = Ankle-Brachial Index; CRP = C-Reactive Protein;
ESR = Erythrocyte Sedimentation Rate; BMI = Body-Mass Index; PAD = Peripheral Artery Disease
[a]Determined using appropriate statistical analyses–Mann-Whitney U-test for continuous variables. Chi-squared test of homogeneity and Fisher exact test
for categorical variables. Significant comparisons are listed. Comparison 1 = Diabetes STI vs Non-Diabetes STI, comparison 2 = Diabetes STI vs Non-Diabetes OM, comparison 3 = Diabetes OM vs Non-Diabetes OM, and comparison 4 = Diabetes OM vs Non-Diabetes STI. The alpha value was divided by four (0.0125)
to accommodate increased chance of type 1 error.
[b]Amputation present at admission
[c] Median and IQR presented for continuous laboratory values
[d]GFR (mL/min) at admission. Categorical distribution of GFR is reported below the median values as number of patients with percentages.

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Table 2. Epidemiologic parameters of erythrocyte sedimentation rate (ESR) in diabetic and non-diabetic patients in the presence or absence of specific comorbidities.

Table 2. Predictive value of erythrocyte-sedimentation rate for osteomyelitis with presence or absence of comorbidities in patients with or without diabetes

Comorbidity	Cutoff[a]	Sensitivity	Sp	PPV[b]	NPV[b]	LR+	LR-	OR[c]	95% CI	AUROC[d]	95% CI[e]
Diabetes[f]											
Neuropathy	61.0	75%	58%	64%	70%	1.78	0.43	**4.16**	(2.58, 6.72)	**0.71**	(0.65, 0.77)
No neuropathy	122.0	50%	44%	50%	44%	0.89	1.14	0.78	(0.20, 3.01)	0.52	(0.31, 0.72)
PAD	66.5	67%	64%	65%	66%	1.86	0.51	**3.65**	(2.17, 6.16)	**0.69**	(0.63, 0.76)
CAD	61.0	80%	55%	64%	73%	1.79	0.36	**4.94**	(2.43, 10.0)	**0.69**	(0.62, 0.77)
Retinopathy	78.5	60%	65%	63%	62%	1.71	0.62	**2.79**	(1.21, 6.39)	**0.72**	(0.51, 0.74)
CKD[g]											
<15	78.5	81%	52%	63%	73%	1.70	0.36	**4.68**	(1.17, 18.7)	**0.67**	(0.51, 0.84)
15-60	118.0	47%	84%	75%	61%	2.93	0.63	**4.63**	(1.71, 12.5)	**0.68**	(0.57, 0.79)
≥60	61.0	65%	69%	68%	67%	2.14	0.50	**4.29**	(2.44, 7.54)	**0.71**	(0.65, 0.78)
No Diabetes[h]											
Neuropathy	19.5	83%	55%	76%	65%	1.84	0.31	**5.91**	(1.70, 20.5)	**0.67**	(0.52, 0.82)
No neuropathy	46.0	50%	77%	53%	75%	2.21	0.65	3.43	(0.94, 12.5)	0.57	(0.38, 0.76)
PAD	44.5	74%	62%	64%	72%	1.93	0.43	**4.55**	(1.18, 17.5)	0.60	(0.41, 0.79)
CAD	44.0	54%	77%	74%	59%	2.37	0.60	**3.97**	(1.12, 14.0)	0.62	(0.45, 0.78)

Sn = sensitivity; Sp = specificity; PPV = positive predictive value; NPV = negative predictive value; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; OR = odds ratio; 95% CI = 95% confidence interval; AUROC = area under receiver operative characteristic curve; PAD = peripheral artery disease; CAD = coronary artery disease; CKD = chronic kidney disease

[a]Cutoff values were determined using receiver operating characteristic analysis. Values are presented as mm/h.

[b]Overall prevalence of osteomyelitis in the cohort of patients with diabetic foot ulcers and non-diabetic foot ulcers were 50.1% and 50% respectively.

[c]Significant odds ratios are in bold.

[d]AUROC values represent the predictive value of the erythrocyte sedimentation rate cutoff values. An AUROC value of 1.0 denotes a perfect test while a value of 0.5 describes a test with an equal chance to predict a true or false positive result. Statistically significant AUROC values are in bold.

[e]AUROC 95% CI were calculated using receiver operating characteristic analysis. Statistical significance was determined if the 95% CI did not include a value of 0.5.

[f]Three-hundred fifty-three patients were in the diabetic cohort.

[g]Different levels of chronic kidney disease were divided by eGFR at admission presented as mL/min.

[h]One-hundred two patients were in the non-diabetic cohort. No patients had retinopathy and too few had CKD for statistical analysis.

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Figure 1a. Scatterplot of erythrocyte sedimentation rate (ESR) values in diabetic and non-diabetic patients with soft-tissue infection or osteomyelitis.

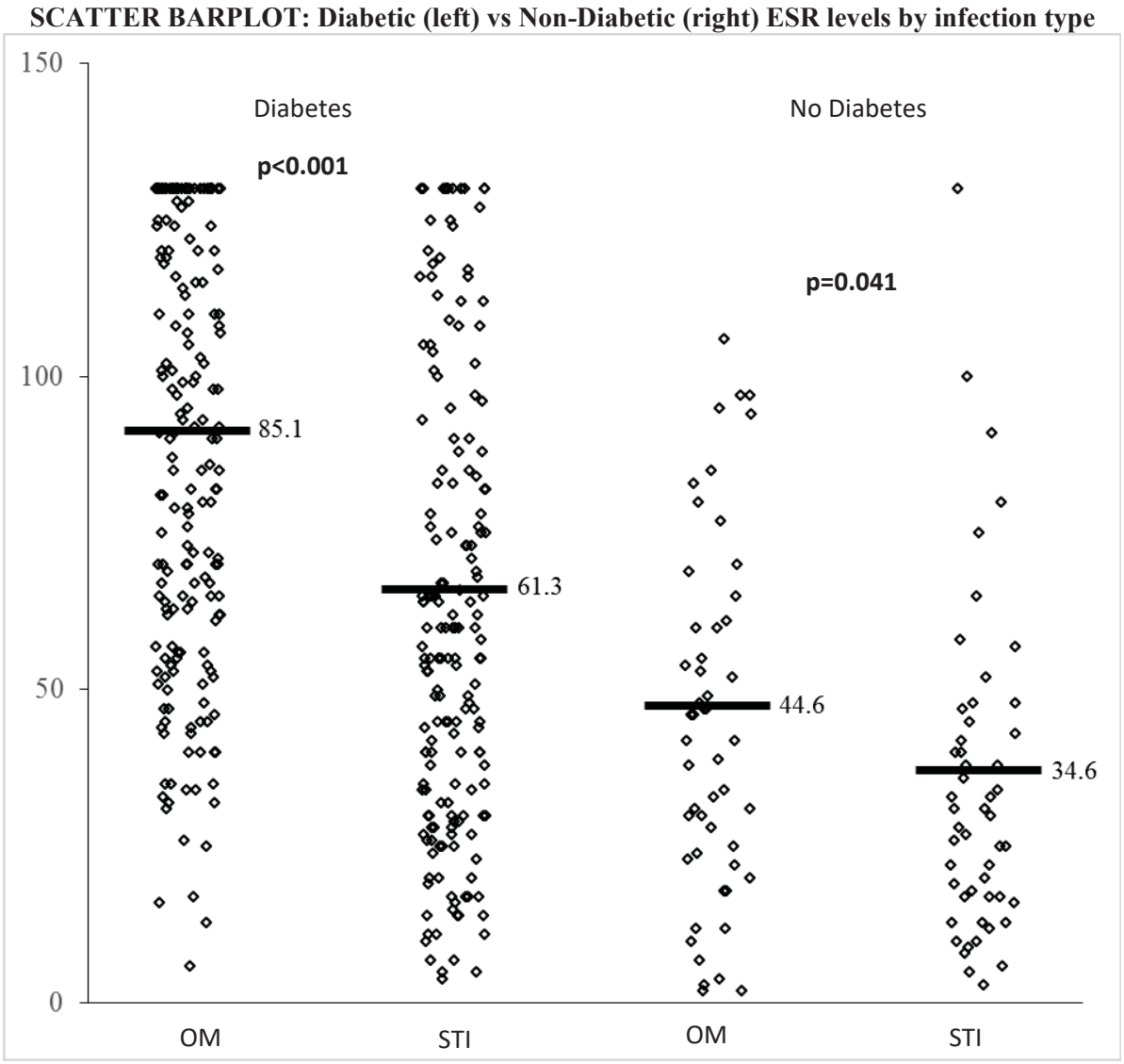

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Figure 1b. Scatterplot of C-reactive protein (CRP) values in diabetic and non-diabetic patients with soft-tissue infection or osteomyelitis.