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Diagnostic Utility of Erythrocyte Sedimentation Rate and C-Reactive Protein in Osteomyelitis of the Foot in Persons Without Diabetes

Easton C. Ryan, BS[1], Junho Ahn, BS[2], Dane K. Wukich, MD[3], Paul J. Kim, DPM, MS, FACFAS[4], Javier La Fontaine, DPM, MS, FACFAS[5], Lawrence A. Lavery, DPM, MPH, FACFAS[5]

[1] *Student, Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, TX*
[2] *Student, Department of Orthopaedic Surgery, University of Texas Southwestern Medical Center, Dallas, TX*
[3] *Surgeon, Department of Orthopaedic Surgery, University of Texas Southwestern Medical Center, Dallas, TX*
[4] *Surgeon, Department of Plastic Surgery, MedStar Georgetown University Hospital, Washington, DC*
[5] *Surgeon, Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, TX*

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ABSTRACT

The aim of the study was to assess the diagnostic value of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels in differentiating foot osteomyelitis (OM) from soft tissue infection (STI) in persons without diabetes. We evaluated 102 patients in a retrospective cohort study of nondiabetic patients admitted to our institution with OM (n = 51) and with STI (n = 51). Patient diagnosis was determined through bone culture and/or histopathology for OM and magnetic resonance scan and/or single-photon emission computed tomography for STI. Cutoffs for ESR and CRP to predict OM as identified by receiver operating characteristic were 45.5 mm/h and 3.45 mg/dL, respectively. The ESR cutoff demonstrated a sensitivity and specificity of 49% and 79%, while the values for CRP were 45% and 71%, respectively. The combined sensitivity and specificity for ESR and CRP were 33% and 84%. The positive and negative predictive values were 68% and 60% for ESR and 61% and 56% for CRP, respectively. In conclusion, ESR and CRP demonstrate poor sensitivity and specificity for detecting OM in the nondiabetic foot. These markers have little diagnostic utility in the nondiabetic foot.

Most of the literature addressing osteomyelitis (OM) of the foot focuses on patients with diabetes mellitus. Little has been published on the topic of ulcers and infected foot ulcers in patients without diabetes. However, OM in persons without diabetes is relatively common, as is foot ulceration. The population-based study by Kremers et al reported the incidence of OM during a 41-year period; there was a 15% incidence of OM of the foot in patients without diabetes (1). Similarly, Zaine et al reported an 18.8% incidence of OM among nondiabetic patients (N = 202) who presented with foot ulcers during a 2-year period to an outpatient wound clinic in Western Sydney, Australia (2). OM of the foot presents a unique diagnostic challenge for healthcare practitioners and often leads to multiple surgeries, prolonged hospitalizations, extended antibiotic exposure, and residual deformity (3–5). Therefore, correct and prompt diagnosis is essential to begin advanced testing and treatment in high-risk patients. Ideally, simple screening tests can help physicians identify high-risk patients.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are inflammatory markers that can be measured by using inexpensive laboratory tests that have shown diagnostic use at other anatomic sites, including vertebral OM, long bone OM, periprosthetic joint infections, and diabetic foot OM (6–13). It seems logical that the data reported from diabetic foot OM studies could be extrapolated to patients without diabetes. However, the optimal cutoff values for ESR and CRP in previous studies to diagnose OM are much higher in patients with diabetic foot OM (14–16). We were unable to identify any reports describing diagnostic parameters for both ESR and CRP in OM of the foot in people without diabetes. The goal of this study was to evaluate the use of ESR and CRP to predict OM in patients presenting with nondiabetic foot infections.

Patients and Methods

After institutional review board approval, a nonblinded retrospective review was performed by E.R. from consecutive medical records of patients who met the following criteria: between 18 and 89 years of age; treated for moderate or severe foot infections in hospital between June 12, 2009, and February 21, 2017; baseline ESR and CRP values analyzed within 72 hours of hospital admission; and no history of diabetes mellitus based on American Diabetes Association diagnostic criteria (17). This includes glycated hemoglobin of 6.5% or greater, or fasting plasma glucose of 126 mg/dL (7.0 mmol/L) or greater, or 2-hour plasma glucose of 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test or

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Address correspondence to: Easton C. Ryan, BS, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390.
E-mail addresses: easton.ryan@utsouthwestern.edu, eastonryn12@gmail.com (E.C. Ryan).

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a patient with classic symptoms of hyperglycemia or hyperglycemic crisis with a random plasma glucose level of 20 mg/dL (11.1 mmol/L) or greater. Demographic data were collected along with a medical and social history, wound characteristics, results of serum laboratory blood draws, clinical outcomes, and surgical and/or vascular interventions. We defined "sensory neuropathy" as abnormal vibration sensation, abnormal sensation with 10-g Semmes-Weinstein monofilament, and/or absent Achilles deep tendon reflexes. We defined "peripheral vascular disease" (PAD) as an ankle to arm systolic blood pressure ratio >0.90 or a history of PAD documented in the patient's chart. Cardiac disease status was determined though history of documented cardiac diagnoses or events in the patient's chart. We defined "foot wounds" as full-thickness lesions involving any portion of the foot or ankle. We defined "foot infection" based on the presence of purulence or at least 2 local signs or symptoms of inflammation.

Patients were included in the study when the treating physician had a high index of suspicion of OM to warrant testing with magnetic resonance scan (MRI), single-positron emission computed tomography (SPECT), or bone biopsy. We used bone biopsy to confirm the diagnosis of OM and MRI and SPECT or negative bone biopsy to identify patients without bone infection because the rate of false-negative results is low (18). Patients were classified as having OM or soft tissue infection (STI) without OM. OM was confirmed with positive bacterial cultures from bone specimens and/or histopathologic changes consistent with OM. Patients with STI demonstrated a negative bone culture and negative histopathology or a negative MRI or negative SPECT study for OM. Patients with other sites of active infection or inflammatory disease processes were excluded. Of the patients with OM, 8 (15.7%) had positive bone cultures without histopathology, 21 (41.2%) had positive histopathology without bone culture results, and 22 (43.1%) had both positive bone culture and histopathology results. Five (9.8%) patients had a positive bone culture and negative histopathology, and 6 (11.8%) had positive histopathology and negative bone culture. Patients with STIs had a bone culture and histopathology or an MRI or SPECT study that was negative for OM. Of the patients with STI, 37 (72.5%) had negative readings on MRI or SPECT for OM without bone culture or histopathology results, 10 (9.8%) patients had negative bone culture and negative bone histopathology without imaging results, and 4 (7.8%) patients had negative imaging and negative bone culture and histopathology. None of patients had positive imaging with negative bone culture or histopathology.

Categorical variables were assessed by using descriptive statistical analyses and are presented as frequencies with percentages. Continuous variables are presented as median values with 25th to 75th interquartile ranges (IQRs) (Table 1). All continuous variables were tested for normality by using Shapiro-Wilk analysis. Continuous variables between OM and STI groups were analyzed by using either Student's t test or Mann-Whitney U test based on parametric criteria. Categorical variables were analyzed by using Pearson χ^2 tests or Fisher's exact test. Sensitivity, specificity, and positive and negative predictive values (PPVs and NPVs) were determined by using contingency table analysis. Various ESR and CRP values were evaluated for sensitivity and specificity (Table 2). Threshold values of ESR and CRP were identified based on the greatest combined value of sensitivity and specificity (Youden J statistic) and confirmed with receiver operating characteristic (ROC) analysis. Areas under the ROC curves (AUROCs) were calculated for both ESR and CRP to evaluate the rate of true predictions of OM. ESR and CRP ROC curves were compared by using the DeLong test (19) (Fig. 1). An α value of 0.05 was used to denote statistical significance. All statistical analyses were performed by using R version 3.3.1 (Vienna, Austria).

Results

One-hundred two patients were evaluated. Fifty-one (50%) patients were diagnosed with OM, and 51 (50%) patients were diagnosed with STI. Fifty-nine (57.8%) patients had neuropathy. The etiologies of neuropathy or nerve injury were 31 (52.5%) patients with idiopathic, 17 (28.8%) patients with spinal cord injury or congenital deficits, 5 (8.5%) patients with posttraumatic nerve injury, 5 (8.5%) patients with alcoholic neuropathy, and 1 (1.7%) patient with sensory loss after stroke. The etiologies of infections were diverse and included trauma in 26 (25.5%) patients (7 puncture wounds, 3 crush injuries, 2 lacerations, 14 other trauma), vascular-related wounds in 25 (24.5%) patients, neuropathic ulcers in 16 (15.7%) patients, footwear-related ulcers in 7 (6.9%)

Table 1
Comparisons of patient factors between nondiabetic patients with soft tissue infection and osteomyelitis

	Overall n = 102		STI n = 51		OM n = 51		
Parameter	Value	IQR	Value	IQR	Value	IQR	p Value*
Patient factors							
Age, median, years	53.5	39 to 61	52	40 to 61	55	38 to 61.5	.901
Male sex, n (%)	76	74.5	39	76.5	37	72.5	.680
Comorbidities, n (%)							
Cardiac disease	48	47.1	22	43.1	26	51.0	.428
Retinopathy	0	0.0	0	0.0	0	0.0	1.000
Neuropathy	55	53.9	20	39.2	35	68.6	.487
Previous ulcer	37	36.3	16	31.4	21	41.2	.303
Previous amputation†	11	10.8	2	3.92	9	17.6	**.026**
PAD	40	39.2	18	35.3	22	43.1	.541
Laboratory values‡							
HbA_{1c} (84)§	5.45	5.1 to 5.7	5.4	4.7 to 5.6	5.6	5.3 to 5.8	.251
eGFR‖							
CKD 5: <15	2	1.96	1	1.96	1	1.96	1.000
CKD 1 to 4: 15 to 60	6	5.88	1	1.96	5	9.80	.205
No CKD: ≥60	94	92.2	49	96.1	45	88.2	.269
Hemoglobin	12.7	11.5 to 13.9	13.3	11.5 to 14.4	12.3	11.6 to 13.5	.141
Serum albumin (95)§	3.7	3.4 to 4.0	3.8	3.4 to 4.28	3.6	3.4 to 3.9	.105
ABI¶	1.18	0.83 to 1.26	1.03	0.53 to 1.25	1.18	1.13 to 1.26	.485
BMI	26.2	23.2 to 31.7	26.0	24.3 to 31.6	26.5	22.5 to 31.4	.462
CRP**	2.05	1.0 to 6.0	1.8	1.0 to 4.8	2.3	0.96 to 7.25	.405
ESR††	33.5	18.3 to 52.8	30.0	17.0 to 44.0	42.0	23.5 to 60.5	**.043**

Abbreviations: ABI, ankle-brachial index; BMI, body mass index; CKD, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; HbA_{1c}, glycosylated hemoglobin; IQR, interquartile range (25th to 75th percentile); OM, osteomyelitis; PAD, peripheral artery disease; STI, soft tissue infection.

* Determined using appropriate statistical analyses: Student's t test and Mann-Whitney U test for continuous variables; χ^2 test of homogeneity and Fisher exact test for categorical variables. Significant values are in bold.

† Amputation present at admission.

‡ Median and IQR presented for continuous laboratory values.

§ Number of patients when N = 102 was not used to arrive at mean laboratory values.

‖ GFR (mL/min) at admission. Categorical distribution of the GFR is reported as number of patients with percentages.

¶ ABI at admission.

** Initial CRP value (mg/dL).

†† Initial ESR value (mm/h).

Table 2
Epidemiologic measures of erythrocyte sedimentation rate/C-reactive protein

Parameter	Sn	Sp	PPV	NPV	LR+	LR–	OR	95% CI
ESR (mm/h)								
> 10	0.88	0.14	0.51	0.54	1.02	0.86	1.19	0.37 to 3.83
> 20	0.78	0.35	0.55	0.62	1.21	0.61	1.98	0.82 to 4.78
> 30	0.65	0.51	0.57	0.59	1.32	0.69	1.91	0.86 to 4.22
> 40	0.53	0.71	0.64	0.60	1.80	0.67	2.70*	1.19 to 6.10*
> 45.5†	0.49	0.79	0.68	0.60	2.08	0.67	3.13*	1.34 to 7.30*
> 50	0.37	0.82	0.68	0.57	2.11	0.76	2.77*	1.11 to 6.93*
> 60	0.25	0.88	0.68	0.54	2.17	0.84	2.57	0.89 to 7.40
> 70	0.18	0.90	0.64	0.52	1.80	0.91	1.97	0.61 to 6.36
CRP (mg/dL)								
> 1.0	0.73	0.31	0.51	0.53	1.06	0.88	1.21	0.51 to 2.84
> 2.0	0.55	0.55	0.55	0.55	1.22	0.82	1.48	0.68 to 3.23
> 3.0	0.45	0.69	0.59	0.56	1.44	0.80	1.80	0.80 to 4.03
> 3.45†	0.45	0.71	0.61	0.56	1.53	0.78	1.97	0.87 to 4.46
> 4.0	0.39	0.71	0.57	0.54	1.33	0.86	1.55	0.68 to 3.53
> 5.0	0.33	0.78	0.61	0.54	1.55	0.85	1.82	0.75 to 4.41
> 6.0	0.31	0.80	0.62	0.54	1.60	0.85	1.87	0.75 to 4.66
> 7.0	0.27	0.84	0.64	0.54	1.75	0.86	2.03	0.77 to 5.38
ESR and CRP‡								
Both	0.33	0.84	0.68	0.56	2.13	0.79	2.69*	1.04 to 6.97*
Either	0.61	0.62	0.62	0.62	1.63	0.63	2.61*	1.17 to 5.80*

Abbreviations: Both, patients with both ESR and CRP are above the threshold value; CI, confidence interval; CRP, C-reactive protein; Either, patients with either ESR or CRP above the threshold; ESR, erythrocyte sedimentation rate; LR–, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; OR, odds ratio; PPV, positive predictive value; Sn, sensitivity; Sp, specificity.

* Statistically significant odds ratios.

† Optimal cutoffs determined by current study.

‡ ESR cutoff of 45.5 mm/h and CRP cutoff of 3.45 mg/dL were used. These values reflect ESR/CRP as a single test.

patients, insect bites in 5 (4.9%) patients, pressure ulcers in 5 (4.9%) patients, postoperative infections in 4 (3.9%) patients, congenital club foot in 2 (2.0%) patients, frostbite in 1 (1.0%) patient, ingrown toe nail in 1 (1.0%) patient, and unknown etiology in 10 (9.8%) patients. Demographic and patient data are summarized in Table 1. There were no significant differences in age ($p = .90$), sex ($p = .68$), or body mass index (BMI) ($p = .46$). The significant differences between study groups were an increased prevalence of a previous amputation on presentation ($p = .03$) and increased ESR ($p = .04$) in the OM group.

In regard to predicting OM in nondiabetic foot infections, the sensitivities, specificities, PPVs, NPVs, positive and negative likelihood ratios (LR+ and LR–, respectively), and odds ratios (ORs) for a range of ESR and CRP values are summarized in Table 2. Optimal cutoff values for ESR and CRP were 45.5 mm/h and 3.45 mg/dL respectively. These cut points demonstrated the greatest Youden index values. Of 51 patients with OM, 26 (49.0%) had ESR values above 45.5 mm/h and 23 (50.1%) had CRP values above 3.45 mg/dL. In contrast, 11 (21.6%) patients with STI had ESR values above the cutoff and 15 (29.4%) had CRP values above the cutoff. As a result, the ESR cutoff had a sensitivity and specificity of 49% and 79%, respectively, and the CRP cutoff had a sensitivity and specificity of 45% and 71% respectively. In addition, LR+ values were 2.08 (95% confidence interval [CI] 1.11 to 3.49) and 1.53 (95% CI 0.91 to 2.58) for ESR and CRP, and LR– values were 0.67 (95% CI 0.53 to 0.94) and 0.78 (95% CI 0.57 to 1.06) for ESR and CRP, respectively.

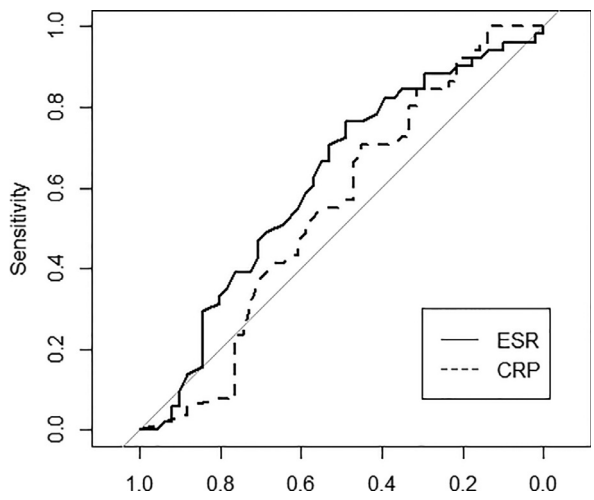

Fig. Receiver operating characteristic (ROC) curve for erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) to diagnose osteomyelitis. The area under the ROC curve (AUROC) for ESR and CRP were 0.62 and 0.55, respectively. DeLong's test did not show any statistical difference between the 2 AUROCs.

The diagnostic values of combining ESR and CRP were evaluated. When "both" ESR and CRP above the thresholds of 45.5 mm/h and 3.45 mg/dL, respectively, were used to identify a "positive result," the sensitivity and specificity of ESR and CRP to detect OM were 33% and 84%, respectively (Table 2). Using either ESR or CRP values above the threshold as a "positive result," the sensitivity and specificity for OM were 61% and 62%, respectively, described as "either" in Table 2. When the test definition of a "positive result" with ESR and CRP is more stringent (requiring both to be above threshold), the combined specificity of the test increases at the cost of sensitivity. When using a more lenient definition, where either a positive ESR or CRP can make the diagnosis, the combined sensitivity is greater at the cost of specificity. Individually, there was no significant difference in predictiveness of OM between ESR and CRP. The AUROCs for ESR were 0.62 and 0.55 for CRP, respectively, and the DeLong test did not show any statistical difference between the 2 AUROCs (Fig., $p = .23$).

Discussion

Foot ulcers and, subsequently, foot OM are commonly associated with diabetes. However, they also occur in people without diabetes due to acquired neuropathy, PAD, pressure-induced tissue injuries, trauma, and puncture wounds (1,14,15,20). Therefore, similar principles to diagnose OM of the foot in diabetic patients may also have value when applied to nondiabetic patient populations. However, to the best of our knowledge, this is the first study to evaluate the utility of both ESR and CRP to distinguish OM from STI in nondiabetic foot infections.

Previous studies have reported success with using ESR and CRP to diagnose vertebral OM, long bone infections and periprosthetic joint infections (6–13). Greidanus et al showed that a threshold of 22.5 mm/h for ESR and a threshold of 1.35 mg/dL for CRP provide excellent diagnostic performance for periprosthetic knee infections (7). Similarly, Ghanem et al established predictive cutoffs of 31 mm/h and 2.05 g/dL for ESR and CRP, respectively, with a 97.6% sensitivity and 81% specificity for periprosthetic hip infections (6).

There are 8 studies that evaluate biomarkers in diabetic foot infections (Table 3) (16,21–28) and 2 studies that evaluate ESR to diagnose OM in nondiabetic foot infections (15,16). Rabjohn et al (16) described 19 patients with OM (n = 12) and STI (n = 7) and demonstrated PPVs and NPVs of 77.8% and 58.3%, respectively, by using an ESR cutoff of 70 mm/h. In contrast, Lavery et al (15) reported PPVs and NPVs of 35.8% and 93.9%, respectively, to predict OM in 69 patients with infected puncture wounds. Our results at the 70-mm/h ESR cutoff value showed a PPV of 64% and an NPV of 52%. This is about the same as making the diagnosis by flipping a coin. Current reports describing inflammatory biomarkers in nondiabetic patients present an unclear message on their utility as tools for evaluating OM of the foot in hospitalized patients.

In the present study, we identified a significantly increased ESR in patients with OM compared with patients with STI. This finding was also reported in a previous study (16). However, despite this statistically significant difference, there was not a reliable relationship between ESR

Table 3
Study design characteristics and results of diabetic foot biomarkers studies

Author, Year, Country	Study Design	OM/STI	Biomarker	Cutoff	Reference Standard
Ertugrul et al,[23] 2009, Turkey	Prospective	24/22	ESR, CRP, WBCs	Several	Histo and/or micro and/or MRI
Fleischer et al,[24] 2009, USA	Retrospective	34/20	ESR, CRP, WBCs, Neutr	ESR > 60 CRP > 3.2 WBCs > 11	Histo and/or 1 imaging modality
Kaleta et al,[25] 2001, USA	Retrospective	19/10	ESR	ESR ≥ 70	Histo or PTB or 2 imaging modalities
Malabu et al,[26] 2007, Saudi Arabia	Prospective	22/21	ESR, WBCs, PLT, RDW	ESR > 70 WBCs > 4.0	PTB or 2 imaging modalities
Michail et al,[27] 2013, Greece	Prospective	27/34	ESR, CRP, WBCs, PCT	Several	PTB and 1 imaging modality
Mutluoglu et al,[28] 2011, Turkey	Prospective	13/11	ESR, CRP, WBCs, PCT	ESR ≥ 47	MRI
Rabjohn et al,[16] 2007, USA	Prospective	66/29	ESR	ESR ≥ 70	Histo

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; histo, histopathology; micro, microbiology; MRI, magnetic resonance scan; Neutr, neutrophil percentage; OM, osteomyelitis; PCT, procalcitonin; PLT, platelet count; PTB, probe to bone test; RDW, red cell distribution width; STI, soft tissue infection; WBC, white blood cell.

and infection type as illustrated by the ROC analysis (Fig. 1). This points to the fact that the distribution of ESR values of patients with STI and OM overlap to a degree that makes correctly predicting bone infection status difficult when using ESR. The cutoffs for ESR and CRP were determined by minimizing the number of false-positive and false-negative results. However, due to the similarity in distributions of ESR and CRP between patients with STI and OM, the optimum cutoff does not perform well to predict infection type. This is demonstrated by the poor sensitivity, specificity, NPV, and PPV values. Furthermore, the LR+ and LR– values represent the probability of an individual with the disease having a test result divided by the probability of an individual without the disease having the test result. For example, an LR+ of 2.0 represents a 2-fold increased probability of the disease compared with baseline probability when the test is positive. In contrast, an LR– value of 0.5 represents a 50% decreased probability of the patient having the disease compared with baseline probability when the test is negative. An LR of 1.0 denotes no change in probability. In clinical practice, LR values are used to determine the pretest diagnostic accuracy after performance of a diagnostic or screening test. The LR values for the optimized cutoffs for ESR and CRP were poor: 2.08 (95% CI 1.11 to 3.49) and 1.53 (95% CI 0.91 to 2.58) for LR+ and 0.67 (95% CI 0.53 to 0.94) and 0.78 (95% CI 0.57 to 1.06) for LR–, respectively. These LR values indicate that ESR and CRP minimally increase pretest diagnostic accuracy. In addition, sensitivity, specificity, NPV, and PPV of the ESR and CRP cutoffs were also poor, corresponding to a diagnostic value for OM comparable to a coin toss. These findings suggest that ESR and CRP measurements are not effective to predict OM versus STI in nondiabetic foot infections.

This study has several advantages. First, we evaluated both ESR and CRP to distinguish OM and STI in nondiabetic foot infections, so both biomarkers could be evaluated from the same patient at the same time and analyzed together. Of note, the mean time for the results of ESR and CRP was 4.5 hours from presentation to the hospital. The collection time is important in order to avoid altering these values, especially CRP, because it can respond quickly once treatment is initiated (29). Second, it is a large study compared with the studies in foot infections without diabetes (69 and 17 cases) (15,16) and in studies of biomarkers in diabetic foot infections (Table 3). Third, the gold standard of bone culture or histopathology was used to confirm the diagnosis of OM as opposed to clinical criteria such as “probe to bone” or imaging through radiography, MRI, or SPECT. We used imaging that has low rates of false-negative and low-negative LR values to identify patients who do not have bone infection. For instance, Butalia and colleagues reported that the LR– value for MRI to diagnose OM was 0.14 (95% CI 0.8 to 0.26) and that the LR+ value was 3.8 (95%CI 2.5 to 5.8) (18). We believe using these reference standards improved the likelihood that people with and without OM were correctly identified. In addition, inclusion and exclusion criteria were followed to ensure that patients with other sites of active infection and acute inflammatory disease processes that could elevate ESR and CRP were excluded in order to accurately assess the predictive capability of the inflammatory biomarkers.

This study had several limitations of this study as well. The first limitation of this study is its retrospective nature, leading to potential measurement and selection bias. Measurement bias was likely because different operational definitions were probably used to define some variables such as cardiac disease. Even though we used the “gold standard” of bone biopsy, the evaluation of histology and cultures are not 100% reliable or accurate. For instance, interobserver variability in the interpretation of bone histology has been reported to be high and could provide inconsistent interpretation of histology specimens (30), especially if it was the primary criteria to define OM. In addition, theoretically patients treated with antibiotics prior to bone culture may have fewer positive cultures. There is a study in patients with diabetic foot OM that shows no difference in bacterial pathogen yield based on the timing of administering antibiotics (31). Most of the work in this area is from vertebral OM. These studies report inconsistent results. There are 2 studies that report higher rates of pathogen identification in patients that were treated with antibiotics before bone cultures were obtained compared with patients without antibiotic exposure (antibiotic treatment 72.0% versus no antibiotics 53.1%, antibiotic treatment 70.0% versus no antibiotics 63%) (32,33), and other studies report reduced pathogen identification if antibiotics are given before culture results are obtained (34,35).

Ideally, all of the same testing procedures would have been performed on every subject to diagnose OM. Because this was a retrospective study, we used a pragmatic approach to define OM and STIs, while using tests that are the gold standard for diagnosis (bone biopsy) and tests that have a very low rate of false negatives (MRI and SPECT) to exclude OM. This could introduce the possibility of selection and measurement bias, particularly with regard to which patients received advanced imaging and biopsy. There were no a priori criteria to order advanced imaging in our institution, so the decision was often based on the treating physician’s index of suspicion for OM. In clinical practice, patients with normal advanced imaging results usually do not undergo bone biopsies to confirm the negative diagnosis unless intraoperative findings warrant the procedure, so bone culture and histology were not available for most patients with negative MRI or SPECT results. In our cohort, only 4 (7.8%) patients had a bone biopsy after a negative imaging study, and all of the results were negative. Previous publications that evaluate biomarkers in diabetic foot OM used a variety of criteria for the reference standard; often 2 reference standards were used, as we did in this study (Table 3).

In summary, the results of this study suggest the use of ESR and CRP is not especially useful to differentiate OM from STI in hospitalized patients without diabetes with moderate and severe foot infections. Although other studies have demonstrated the diagnostic utility of these biomarkers to predict OM in the diabetic foot and at other

anatomic sites, it does not seem that these results can be extrapolated to moderate and severe foot infections in people without diabetes. Application of ESR and CRP cutoffs by healthcare professionals in nondiabetic foot infections to predict OM may lead to misdiagnosis, delaying the onset of important and possible limb-saving treatment. Further prospective research is needed to establish the diagnostic utility, or lack thereof, of ESR and CRP and other biomarkers in the nondiabetic foot infections.

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