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The infected diabetic foot: Modulation of traditional biomarkers for osteomyelitis diagnosis in the setting of diabetic foot infection and renal impairment

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Abstract

The objective of this paper was to investigate erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) in diagnosing pedal osteomyelitis (OM) in patients with and without diabetes, and with and without severe renal impairment (SRI). This was a retrospective cohort study of patients with moderate and severe foot infections. We evaluated three groups: Subjects without diabetes (NDM), subjects with diabetes and without severe renal insufficiency (DM-NSRI), and patients with diabetes and SRI (DM-SRI). SRI was defined as eGFR <30. We evaluated area under the curve (AUC), cutoff point, sensitivity and specificity to characterize the accuracy of ESR and CRP to diagnose OM. A total of 408 patients were included in the analysis. ROC analysis in the NDM group revealed the AUC for ESR was 0.62, with a cutoff value of 46 mm/h (sensitivity, 49.0%; specificity, 76.0%). DM-NSRI subjects showed the AUC for ESR was 0.70 with the cutoff value of 61 mm/h (sensitivity, 68.9%; specificity 61.8%). In DM-SRI, the AUC for ESR was 0.67, with a cutoff value of 119 mm/h (sensitivity, 46.4%; specificity, 82.40%). In the NDM group, the AUC for CRP was 0.55, with a cutoff value of 6.4 mg/dL (sensitivity, 31.3%; specificity, 84.0%). For DM-NSRI, the AUC for CRP was 0.70, with a cutoff value of 8 mg/dL (sensitivity, 49.2%; specificity, 80.6%). In DM-SRI, the AUC for CRP was 0.62, with a cutoff value of 7 mg/dL (sensitivity, 57.1%; specificity, 67.7%). While CRP demonstrated relatively consistent utility, ESR's diagnostic cutoff points diverged significantly. These results highlight the necessity of considering patient-specific factors when interpreting ESR results in the context of OM diagnosis.

KEYWORDS
biomarker, CRP, diabetic foot, ESR, osteomyelitis, renal impairment

Key Messages

- Variable Diagnostic Accuracy of ESR and CRP: The findings reveal that while both ESR and CRP were evaluated as potential biomarkers, their diagnostic accuracy varied across different patient groups.
- Distinct Patient Groups Evaluated: The study focused on three distinct patient groups: subjects without diabetes (NDM), subjects with diabetes but without severe renal insufficiency (DM-NSRI), and patients with diabetes and severe renal impairment (DM-SRI).
- Diagnostic Parameters for ESR: The diagnostic parameters for ESR were evaluated in each patient group. The areas under the curve (AUC) were determined to quantify the overall diagnostic accuracy. The cutoff values, sensitivity and specificity were also calculated. The AUC values ranged from 0.62 to 0.70 for different patient groups, indicating varying degrees of accuracy.
- Diagnostic Parameters for CRP: Similar to ESR, the diagnostic parameters for C-reactive protein (CRP) were assessed. The AUC values for CRP ranged from 0.55 to 0.70 across the patient groups. Cutoff values, sensitivity and specificity were also reported for each patient group.
- Patient-Specific Interpretation of ESR: An important finding is the divergence of diagnostic cutoff points for ESR across different patient groups. This suggests that patient-specific factors, such as the presence/absence of diabetes and severe renal impairment, can significantly influence the interpretation of ESR results in the context of diagnosing pedal osteomyelitis.

1 | INTRODUCTION

Osteomyelitis poses a substantial clinical challenge due to its potential for serious complications and the interplay of underlying health conditions. Accurate and timely diagnosis is critical to guide appropriate therapeutic interventions and minimize patient morbidity. Erythrocyte sedimentation rate (ESR) and CRP, two widely utilized biomarkers of inflammation, have been proposed as potential aids in osteomyelitis diagnosis, offering a non-invasive approach to aid clinical decision-making.

It is well understood that the presence of comorbidities can alter the serum levels of ESR and CRP.[1–4] The complexity of osteomyelitis diagnosis is increased by the presence of comorbidities such as diabetes and renal impairment.[5,6] However, the influence of severe renal impairment on the diagnostic utility of ESR and CRP in osteomyelitis remains incompletely understood. We conducted a retrospective cohort study involving patients both with and without diabetes, as well as those with and without severe renal impairment. The objective of this study was to evaluate the diagnostic utility of ESR and CRP in these groups.

2 | METHODS

This was a retrospective cohort study of patients admitted to hospital with moderate or severe diabetic foot infections. Before initiating the study, we obtained Institutional Review Board approval. We evaluated patients between 18 and 89 years of age, and defined diabetes based on American Diabetes Association criteria. Osteomyelitis diagnosis was based on a positive culture or histology.[7,8] Patients with a soft tissue infection (STI) had either a negative bone biopsy or negative MRI or SPECT CT. We stratified patients into three groups: NDM, DM-NSRI and DM-SRI. We defined severe renal impairment as patients having an estimated glomerular filtration rate (eGFR) <30. At the time of admission, CRP and ESR were routinely ordered as part of standard care. In our population, no nondiabetic patient had severe renal impairment and, therefore, this group could not be evaluated.

Continuous variables were tested for normality using quantile-quantile, histogram and Shapiro–Wilk analysis. As most of these variables did not follow a normal distribution, descriptive statistical analyses were used to

determine median values of continuous variables with 1st and 3rd interquartile range (IQR) and frequencies of categorical variables. Continuous variables between groups were compared using either Student *t*-test or Mann–Whitney *U*-test. Categorical variables were analysed using Pearson χ^2 test or Fisher exact test when appropriate. Contingency tables were used to calculate descriptive epidemiologic measures (odds ratios, sensitivity, specificity, etc.).

Receiver-operating characteristic (ROC) curve analysis was utilized for both ESR and CRP to determine performance of each test in detecting of OM. In our analysis, standard interpretation of area under the curve (AUC) was used: less than 0.7, acceptable; 0.7–0.8, fair; and greater than 0.8, good accuracy.[9] Optimal threshold values, defined as those with the lowest rates of false results, for ESR and CRP were identified by selecting the thresholds with the maximum Youden's *J*-statistic value and then confirmed through ROC analysis.[10] An alpha value of 0.05 was used in all statistical analysis to denote significance. Logistic regression was performed to analyse the interaction between ESR, CRP and SRI. The AUC, cutoff point, sensitivity and specificity were analysed by ROC curve analysis. All statistical analyses were performed using RStudio version 3.3.1 (Vienna, Austria).[11] Figures 1 and 2.

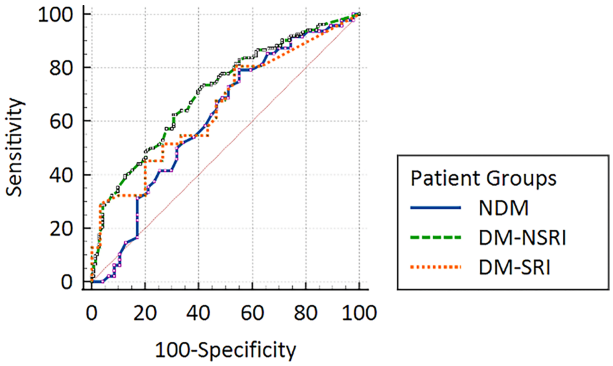

FIGURE 1 Combined ROC plots for erythrocyte sedimentation rate by patient group.

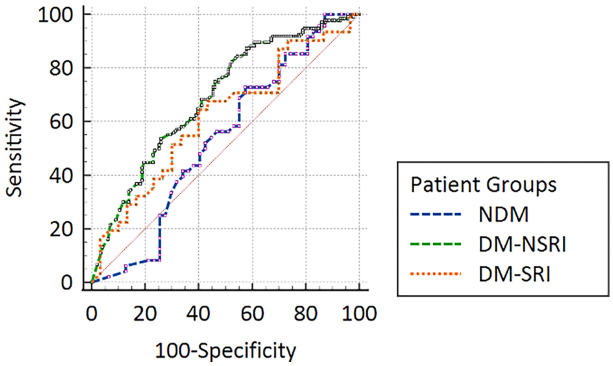

FIGURE 2 Combined ROC plots for c-reactive protein by patient group.

3 | RESULTS

We included 101 nondiabetic patients without severe renal impairment (NDM), 245 DM-NSRI and 60 DM-SRI. Demographic and patient data are summarized in Table 1. The sensitivities, specificities, PPVs, NPVs, positive and negative likelihood ratios (LR+ and LR–, respectively), and AUCs for ESR and CRP are summarized in Table 2.

For patients without diabetes, optimal cutoff values for ESR and CRP were 46 mm/h and 6.4 mg/dL. These cut points demonstrated the greatest Youden index values. The ESR cutoff had a sensitivity and specificity of 49% and 76%, and the CRP cutoff had a sensitivity and specificity of 31.3% and 84%, respectively. In addition, LR + values were 2.0 and 2.0 for ESR and CRP, and LR– values were 0.67 and 0.82 for ESR and CRP. The AUC of ESR and CRP to predict OM in nondiabetic foot infections was 0.62 and 0.55.

For people with diabetes that did not have severe renal insufficiency, optimal cutoff values for ESR and CRP were 61 mm/h and 8 mg/dL. The ESR cutoff had a sensitivity and specificity of 68.9% and 61.8%, and the CRP cutoff had a sensitivity and specificity of 49.2% and 80.6%. In addition, LR+ values were 1.8 and 2.5 for ESR and CRP, and LR– values were 0.5 and 0.63 for ESR and CRP. The AUC of ESR and CRP to predict OM was 0.7 and 0.7, respectively.

For people with diabetes with severe renal insufficiency, optimal cutoff values for ESR and CRP were 119 mm/h and 7 mg/dL. The ESR cutoff had a sensitivity and specificity of 46.4% and 82.4%, and the CRP cutoff had a sensitivity and specificity of 57.1% and 67.7%, respectively. In addition, LR+ values were 2.6 and 1.8 for ESR and CRP, and LR– values were 0.65 and 0.63 for ESR and CRP. The AUC of ESR and CRP to predict OM was 0.67 and 0.62.

When we examined the diagnostic value of combining ESR and CRP, the highest AUC (0.72) was found when 'both' ESR and CRP were above the thresholds of 62 mm/h and 3.7 mg/dL in patients with diabetes and without severe renal impairment. The sensitivity and specificity of ESR and CRP to detect OM were 66.1% and 67.8% (Table 2). For patients with diabetic foot infections with severe renal impairment the AUC for both ESR and CRP was 0.68 with a sensitivity of 92.9% and 35.3%. For nondiabetic foot infections, the AUC for both ESR and CRP was 0.61 with a sensitivity of 62.7% and 66.0%.

TABLE 1 Comparison of patient factors between diabetics with and without severe renal impairment.

Variable	NDM $N = 101$	DM-NSRI $N = 245$	DM-SRI $N = 62$	p
Demographic				
Age, years of age	50.0 [39.0;61.0]	52.7 [45.0;60.0]	54.7 [45.2;63.0]	0.048
BMI, kg/m^2	28.0 [23.2;30.8]	32.2 [25.8;36.3]	32.6 [26.3;38.0]	<0.001
Male	76 (75.2%)	190 (77.6%)	39 (62.9%)	0.028
Patient medical history				
Cardiac disease	47 (46.5%)	194 (79.2%)	60 (96.8%)	<0.001
Retinopathy	0 (0%)	61 (24.9%)	26 (41.9%)	<0.001
Neuropathy	55 (54.5%)	219 (89.4%)	59 (95.2%)	<0.001
PAD	40 (39.6%)	164 (66.9%)	54 (87.1%)	<0.001
Previous amputation	11 (10.9%)	93 (38.0%)	22 (35.5%)	<0.001
Previous ulcer	37 (36.6%)	165 (67.3%)	35 (56.5%)	<0.001
Osteomyelitis (%)	47 (46.5%)	122 (49.8%)	28 (45.2%)	NS
Laboratory values				
GFR, mL/min	60.0 [60.0;60.0]	60.0 [60.0;60.0]	12.5 [7.0;19.0]	<0.001
Glycated Haemoglobin	5.5 [5.1;5.7]	9.2 [7.6;11.3]	7.2 [6.1;8.7]	<0.001
CRP, mg/dL	2.1 [1.0;6.2]	3.9 [1.2;9.7]	5.5 [2.1;13.2]	<0.001
ESR, mm/hr	33.0 [18.0;53.0]	64.0 [40.0;100.0]	94.0 [67.0;128.8]	<0.001
WBC, 10^9/L	9.5 [6.6;11.9]	10.5 [7.4;12.6]	11.5 [7.9;14.0]	0.020
Albumin, g/dL	3.7 [3.4;4.0]	3.4 [2.9;3.8]	3.2 [2.8;3.6]	<0.001

Note: Continuous variables represented as median and quartiles 1 and 3. Categorical variables are represented as *n* and percentage. Wilcoxon rank-sum test; Pearson's Chi-squared test. NS, not significant (>0.05).

TABLE 2 Diagnostic performance of biomarkers to diagnose osteomyelitis.

DFO Biomarker	AUC	Cutoff	Sensitivity	Specificity	+LR	−LR	PPV	NPV
No diabetes (NDM)								
CRP	0.55	6.4 mg/dL	31.3%	84.0%	1.96	0.82	66.7%	54.6%
ESR	0.62	46 mm/h	49.0%	76.0%	2.04	0.67	67.6%	59.4%
ESR × CRP	0.61	42, 1.2	62.7%	66.0%	1.84	0.57	65.3%	63.5%
Diabetes and no severe renal insufficiency (DM-NSRI)								
CRP	0.70	8 mg/dL	49.2%	80.6%	2.53	0.63	71.4%	61.49%
ESR	0.70	61 mm/h	68.9%	61.8%	1.8	0.5	64.1%	66.7%
ESR × CRP	0.72	62, 3.7	68.9%	65.0%	1.97	0.48	66.1%	67.8%
Diabetes and severe renal insufficiency (DM-SRI)								
CRP	0.62	7 mg/dL	57.1%	67.7%	1.77	0.63	59.3%	65.7%
ESR	0.67	119 mm/h	46.4%	82.40%	2.64	0.65	68.4%	65.4%
ESR × CRP	0.68	67, 0.2	92.9%	35.3%	1.44	0.2	54.2%	85.7%

4 | DISCUSSION

The presence of osteomyelitis guides important clinical decisions like antibiotic duration and surgical intervention.[12–15] A missed diagnosis of OM can delay initiation of treatments and allow the infection to spread.[16,17] ESR and CRP are the most common biomarkers in the literature to diagnose diabetic foot

osteomyelitis.[1,4,18–34] The influence of renal impairment and diabetes status on biomarker accuracy in the diagnosis of osteomyelitis has been sparsely studied in the literature. Only one study has previously evaluated biomarkers in diabetic patients with SRI,[4] and one study evaluated foot infections in people with no diabetes.[35]

In this retrospective cohort study, we assessed the diagnostic utility of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in identifying pedal osteomyelitis (OM) across distinct patient subsets characterized by diabetes status and severe renal impairment (SRI). We analysed data from 408 patients with moderate to severe foot infections, classified into three groups: subjects without diabetes (NDM), subjects with diabetes but without severe renal insufficiency (DM-NSRI) and patients with diabetes and SRI (DM-SRI), with SRI defined as an eGFR <30

For ESR, the ROC analysis demonstrated diverse discriminatory accuracy across the patient groups. Among NDM patients, the area under the curve (AUC) was 0.62, with a sensitivity of 49.0% and specificity of 76.0%, at a cutoff value of 46 mm/h. DM-NSRI subjects exhibited improved diagnostic performance with an AUC of 0.70, a sensitivity of 68.9%, specificity of 61.8% and a cutoff value of 61 mm/h. In the DM-SRI cohort, the AUC was 0.67, sensitivity was 46.4%, specificity was 82.4%, and the cutoff value was notably elevated at 119 mm/h.

Regarding CRP, the AUC values presented consistent patterns across the patient subsets. In the NDM group, the AUC was 0.55, sensitivity was 31.3%, specificity was 84.0%, and the cutoff value was 6.4 mg/dL. For DM-NSRI, CRP exhibited an AUC of 0.70, sensitivity of 49.2%, specificity of 80.6% and a cutoff value of 8 mg/dL. In DM-SRI, the AUC was 0.62, sensitivity was 57.1%, specificity was 67.7%, and the cutoff value stood at 7 mg/dL.

Our study underscores the distinct variations in ESR cutoff points within the three evaluated patient groups, highlighting the influence of diabetes and renal impairment. Conversely, CRP displayed comparable patterns across these groups. Overall, the AUC values for both ESR and CRP demonstrated acceptable or poor discriminatory power in this analysis.[9]

5 | CONCLUSIONS

The diagnostic landscape for pedal osteomyelitis is complex, influenced by underlying health conditions. While CRP demonstrated relatively consistent utility, ESR's diagnostic cutoff points diverged significantly. These results highlight the necessity of considering patient-specific factors when interpreting ESR results in the context of OM diagnosis. In summary, this study enhances our understanding of the diagnostic characteristics of ESR and CRP in the context of pedal osteomyelitis, illuminating their potential utility across distinct patient subsets. As healthcare decisions hinge on accurate diagnostic tools, our findings contribute to refining diagnostic strategies and ensuring optimal patient care in challenging clinical scenarios. Further research is warranted to develop enhanced diagnostic approaches that consider the intricate interplay of medical conditions influencing these biomarkers' performance.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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