Utilization of Inflammatory Biomarkers to Guide Clinical Decision Making in Diabetic Foot Tissue Loss

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Statement of Purpose and Literature Review

The laboratory analysis of inflammatory biomarkers for the diagnosis of infection is widely considered to be standard practice. This has been previously well investigated primarily with respect to the diagnosis of a specific aspect of infection (such as the presence/absence of osteomyelitis) or to demonstrate the association between initial disease presentation and final clinical outcome [1-7]. However, it has been our clinical experience that the primary points of medical decision making on the initial presentation of diabetic foot infection are 1) whether or not the patient requires in-patient management or can be managed as an outpatient, and 2) whether or not the patient requires operative intervention for the infection.

Therefore, the objective of this investigation was to evaluate the association between inflammatory biomarkers on initial presentation against these two medical decision points in the setting of diabetic foot infection (in-patient admission and operative intervention).

Methodology

A retrospective analysis was performed of consecutive subjects presenting to the emergency department of an urban tertiary care hospital with the clinical presentation of a diabetic foot infection. This included those with cellulitis, suspected abscess, acute/chronic wound, and/or osteomyelitis. Inclusion criteria were the presence of diabetes, emergency room consultation by the Foot and Ankle Surgery service, and the performance of a white blood cell count (WBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the emergency department within 24 hours of admission. The evaluated outcomes were whether the subject was admitted for in-patient management and whether the subject underwent surgical intervention for the infection.

Calculations of sensitivity, specificity, positive predictive value and negative predictive value were performed for each biomarker at several different thresholds. For the calculations, admission (vs. not admitted) and operative intervention (vs. no operative intervention) were considered the outcome traits of interest, while the laboratory values were considered the diagnostic test. Values over the identified thresholds indicated a positive test.

Results

Forty-eight patients met criteria and were included in this analysis. Results are depicted in the two tables below for in-patient admission (left table) and operative intervention (right table). The sensitivity of a diagnostic test is generally considered to be the ability of the test (i.e. an elevated laboratory value in this study) to appropriately identify subjects with the trait of interest. For this study, for example, the **sensitivity** of the WBC would essentially be the ability of the WBC to correctly identify how many patients were admitted or went to the OR. The **specificity** of a diagnostic test, on the other hand, is considered the ability of a diagnostic test to appropriately identify subjects without the trait of interest. In other words, how well did the diagnostic test identify which patients would not be admitted or would not go to the OR? In terms of analysis, a "gold standard"-level diagnostic test would be expected have levels of both sensitivity and specificity greater than 80%.

No measurement at any threshold met this definition of both sensitivity and specificity higher than 80%. In fact, only ESR at 30mm/hr and CRP at 0.4mg/dL met this for sensitivity for both admission and need for operative intervention. We did not observe any value of specificity over 80% for any laboratory measurement, although WBC at 11.0K/mm3 and CRP at 14mg/dL came close. As might be expected, levels of sensitivity for ESR and CRP were relatively high. These are generally considered to be relatively sensitive measures for inflammation although not necessarily specific for infection. Interestingly, however, levels of sensitivity decreased with higher thresholds, with levels of specificity increasing with higher thresholds.

The **positive predictive value** is the probability that subjects with a positive diagnostic test (i.e. a laboratory value above the listed threshold) will actually have the outcome of interest (admission and OR intervention in this study). The **negative predictive value** is conversely the probability that subjects with a negative diagnostic test (i.e. a laboratory value below the listed threshold) will not have the outcome of interest (no admission and no OR intervention in this study). Levels of positive predictive value were generally high throughout, while levels of negative predictive value were low, particularly for the in-patient admission.

These numbers might not be a surprise considering our inclusion cohort. One limitation of this study is the relatively high pre-test probability of this study population. In other words, diabetic patients presenting with clinical suspicion of infection are probably more likely than less likely to be admitted, and are also probably more likely to undergo surgical intervention. Populations that have a relatively high prevalence of the outcome of interest (admission and operative intervention in this study) are likely to have high positive predictive values and low negative predictive values. This likely also explains our uniform specificity measurements as most subjects in this study were admitted.

Need for Admission (n=48)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
WBC ≥11.0 K/mm3	39%	50%	95%	3%
ESR ≥30mm/hr	82%	50%	97%	11%
ESR ≥70mm/hr	43%	50%	95%	3%
CRP ≥0.4mg/dL	93%	50%	98%	25%
CRP ≥5.0mg/dL	65%	50%	97%	6%
CRP ≥14.0mg/dL	20%	50%	90%	3%

Need for OR (n=48)	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
WBC ≥11.0 K/mm3	43%	77%	83%	33%
ESR ≥30mm/hr	88%	27%	73%	50%
ESR ≥70mm/hr	59%	43%	71%	30%
CRP ≥0.4mg/dL	94%	8%	73%	33%
CRP ≥5.0mg/dL	63%	38%	73%	28%
CRP ≥14mg/dL	18%	79%	67%	28%

Discussion

As with any scientific investigation, critical readers are encouraged to review the study design and specific results in order to reach their own conclusions, while the following represents our conclusions based on the data. As scientists, we also never consider data to be definitive, but do think that these results are worthy of attention and future investigation:

The results of this investigation found that inflammatory biomarker laboratory values had relatively modest measures of sensitivity and specificity with respect to identifying which patients seen in the emergency department with diabetic foot disease might go on to in-patient admission and/or requiring operative intervention. Although these tests should remain a part of medical decision making, it does not appear as though they should drive the entire decision. It is our hope, however, that this information might lead to other investigations toward the development of objective admission criteria and surgical indication criteria that will aid foot and ankle surgeons with evaluating diabetic patients at risk for infection.

References

[1] Michail M, Jude E, Liaskos C, Karamagiolis S, Makrilakis K, Dimitroulis D, Michail O, Tentolouris N. The performance of serum inflammatory markers for the diagnosis and follow-up of patients with osteomyelitis. Int J Lower Extrem Wounds. 12(2): 94-99, 2013.

[2] Ong E, Farran S, Salloum M, Gardner S, Giovinco N, Armstrong DG, Matthias KE, Nix DE, Mohajer MA. Does everything that's counted count? Value of inflammatory markers for following therapy and predicting outcome in diabetic foot infection. Int J Lower Extrem Wounds. 16(2): 104-7, 2017.

[3] Khodaee M, Lombardo D, Montgomery LC, Lyon C, Montoya C. What's the best test for underlying osteomyelitis in patients with diabetic foot ulcers? J Fam Pract. 64(5): 309-21, 2015.

[4] van Asten SAV, Jupiter DC, La Fontaine J, Davis KE, Lavery LA. Erythrocyte sedimentation rate and C-reactive protein to monitor treatment outcomes in diabetic foot osteomyelitis. Int Wound J. 14(1): 142-8, 2017.

[5] Tabur S, Eren MA, Celik Y, Dag OF, Sabuncu T, Sayiner ZA, Savas E. The major predictors of amputation and length of stay in diabetic patients with acute foot ulceration. Wien Klin Wochenschr. 127(1-2): 45-50, 2015.

[6] Famanujam C, Han D, Zgonis T. Medical imaging and laboratory analysis of diagnostic accuracy in 107 consecutive hospitalized patients with diabetic foot osteomyelitis and partial foot amputations. Foot Ankle Spec. 11(5): 433-44, 2017.

[7] Lin Z, Vasudevan A, Tambyah PA. Use of erythrocyte sedimentation rate and C-reactive protein to predict osteomyelitis recurrence. J Orthop Surg. 24(1): 77-83, 2016.