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Erythrocyte Sedimentation Rate and C-reactive Protein to monitor treatment outcomes in diabetic foot osteomyeltis

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Introduction

Approximately 20% of the patients with diabetic foot infections develop osteomyelitis (DFO) [1]. The occurrence of osteomyelitis further complicates the treatment course of these patients, with prolonged antibiotic therapy, surgical interventions including amputations [2] and therapy related adverse events including kidney injury and the development of bacterial resistance. Based on limited available data, the erythrocyte sedimentation rate (ESR) appears to be the best biomarker to diagnose patients with osteomyelitis [3]. Elevated levels of other inflammatory markers such as C-reactive protein (CRP) and procalcitonin seem to be less informative [3, 4]. The latter markers might be used in the acute phase of the disease, but revert to normal typically within a week of treatment. The ESR may be useful in monitoring response to therapy, as it tends to normalize more slowly [5]. However, this hypothesis still needs to be confirmed in larger studies with a biopsy proven diagnosis of diabetic foot osteomyelitis. In this retrospective study, we aimed to evaluate and compare the roles of the inflammatory markers ESR and CRP in monitoring remission of DFO.

Methods

- We screened 150 medical records of patients admitted to our hospital with DFO between January 1, 2010 and December 31, 2014.
- Inclusion Criteria: positive diagnosis of DFO through bone cultures and/or histopathology, age between 18 to 89 years of age and a follow-up period of 12 months.
- We screened the medical records for the clinical outcomes wound healing, re-infection, recurrent ulceration, re-hospitalization, additional surgery on the study foot, re-amputation and death.
- We defined our primary outcome, DFO remission, as wound healing during follow-up without recurrent infection at the same site as the index wound.
- We retrieved and summarized all weekly values of ESR and CRP for a period of 6 weeks after initial diagnosis, and subsequently all the available monthly values up to 1 year.
- The relationship of the various covariates and the categorical outcomes listed above was assessed using t-test/ANOVA or Fisher's exact test/chi-squared test, as appropriate.
- We grouped patients into those who did, and those who did not reach the endpoint for remission, wound healing, reinfection, recurrent ulceration, re-hospitalization, additional surgery, re-amputation and death, and evaluated associations with biomarkers.
- We then plotted the mean marker level of patients within an outcome group for each time frame.

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Table 1: Diagnosis of diabetic foot osteomyelitis (N=122)

Route of obtained bone sample	
Percutaneous	22 (18.0)
Intraoperative specimen	100 (82.0)
Confirmation of diagnosis	
Positive culture	22 (18.0)
Positive histopathology	35 (28.7)
Positive culture and histopathology	65 (53.3)

Table 2. Characteristics of enrolled patients at admission

	Total	DFO Remission*	No Remission	P value
	N=122	Yes (N=46)	No (N=76)	
Mean age, in years	53.3±10.7	53.9±10.3	53.0±11.0	0.65
Sex, male	95 (77.9)	37 (80.4)	58 (76.3)	0.59
History of Renal Disease	51 (41.8)	15 (32.6)	36 (47.4)	0.11
Stage 2**	7 (4.9)	3 (6.5)	4 (5.3)	
Stage 3	26 (21.3)	9 (19.6)	17 (22.4)	
Stage 4	5 (4.1)	1 (2.2)	4 (5.3)	
Stage 5	13 (10.7)	2 (4.3)	11 (14.5)	
Mean HbA1c, %, (mmol/mol)	9.2(77)±2.3	9.6(81)±2.4	8.9(74)±2.2	0.11
Mean Prealbumin, mg/dL	15.1±6.7	17.1±6.6	14.3±6.6	0.15
Mean GFR, mL/min/1.73m^2	50.9±16.7	54.8±12.7	48.6±18.5	0.049
Mean Hb, g/dL	11.4±3.4	12.1±4.8	11.0±2.1	0.08
Mean ESR, mm/hr	86.2±34.2	83.1±32.6	88.01±35.2	0.44
Mean CRP, mg/dL	12.3±17.9	12.5±22.2	12.2±14.8	0.94
Mean depth of wound, mm	7.8±6.9	6.2±3.7	8.6±8.0	0.40
Positive PTBT	56 (45.9)	17 (37.0)	39 (51.3)	0.20
Results X-ray at admission				
No osteomyelitis	20 (16.4)	8 (17.4)	12 (15.8)	0.06
Osteomyelitis	51 (41.8)	25 (54.3)	26 (34.2)	
Indeterminate	50 (41.0)	13 (28.3)	37 (48.7)	
Mean wound duration before admission, in days	72±204	103±298	53±114	0.19
Ulcer location				
Small toes	48 (39.3)	18 (39.1)	30 (39.5)	0.22
Great toe	27 (22.1)	14 (30.4)	13 (17.1)	
Metatarsals	34 (27.9)	12 (26.1)	22 (28.9)	
Midfoot/dorsum	4 (3.3)	0 (0)	4 (5.3)	
Heel	9 (7.4)	2 (4.3)	7 (9.2)	
Antibiotics before admission	40 (32.8)	14 (30.4)	26 (34.2)	0.67

Figure 1: Trajectories of average Erythrocyte Sedimentation Rate and C-reactive protein within the outcome groups DFO remission and re-amputation over 12 months follow-up.

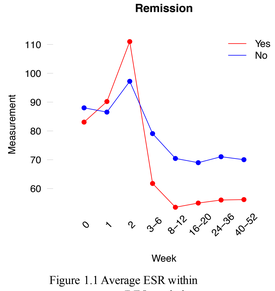

Figure 1.1 Average ESR within outcome group DFO remission

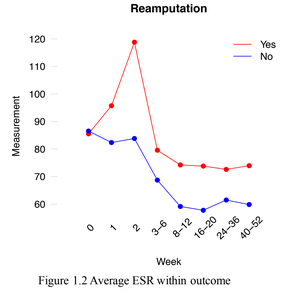

Figure 1.2 Average ESR within outcome group re-amputation

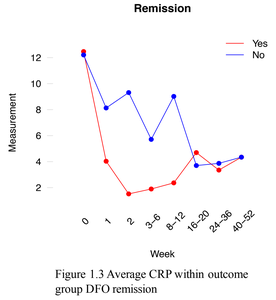

Figure 1.3 Average CRP within outcome group DFO remission

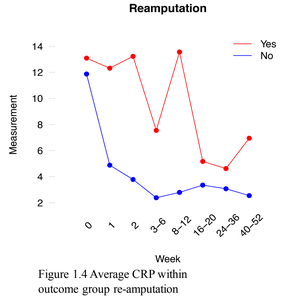

Figure 1.4 Average CRP within outcome group re-amputation

Results

- Of the 122 included patients, confirmation of DFO diagnosis was obtained during surgery in 100 patients (82.0%, table 1).
- More than half of the enrolled patients had a combination of positive culture results and histopathology criteria consistent with DFO (Table 1).
- Ninety-two patients (75.4%) started with the empiric treatment of vancomycin and piperacillin/tazobactam at admission.
- Factors significantly associated with DFO remission ($p<0.05$) were a lower mean white blood count (WBC) at admission ($p=0.006$) and a higher mean glomerular filtration rate (GFR) at admission ($p=0.049$).
- Factors significantly associated with healing (n=54, 44.3%) were: a lower WBC ($p=0.004$), a higher GFR ($p=0.01$), longer mean wound duration before admission ($p=0.01$), an ulcer located on the great toe ($p=0.03$), and a higher mean HbA1c at admission ($p=0.03$).
- ESR and CRP at baseline were not associated with DFO remission ($p=0.44$ and $p=0.94$ respectively) or with healing ($p=0.61$ and $p=0.99$ respectively).
- The mean ESR of the 46 patients who had remission of DFO declined within 6 weeks of therapy while the mean ESR of the group that did not heal or developed a new infection tended to normalize more slowly (Figure 1).
- The mean CRP of the patients who needed additional amputation during follow up is higher (9.56 mg/dL) than in the patients who did not need additional amputations (4.33mg/dL, figure 1).

Discussion

- Patients with DFO have longer hospitalizations and longer treatment courses compared to patients with soft tissue infections, which contributes to the high economic burden associated with diabetic foot ulcers [2, 6].
- Treatment complications like antibiotic resistance, kidney injury and catheter related adverse events limit therapy options for these patients and worsen the prognosis for cure [7].
- Most treatment choices are based on experience and recommendations rather than on high quality evidence.
- A major difficulty is how to determine resolution of osteomyelitis, and subsequently success of treatment.
- Important limitations of our study design include selection of surrogate clinical outcomes (wound healing and no re-infection) to measure DFO remission, the retrospective nature of the study, and unmeasured patient variables such as compliance, off loading, microvascular status, neuropathy and nutritional status.
- The results of our study suggest a predictive role for both ESR and CRP when monitoring success of therapy in DFO.

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