



INVESTIGATIONS THAT PREDICT THE OCCURRENCE OF OSTEOMYELITIS AND PERIPHERAL ARTERIAL DISEASE IN GRADE 3 AND GRADE 4 DIABETIC FOOT ULCERS.

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ABSTRACT **Background:** The global prevalence of diabetes and its complications has surged, escalating from 2.8% in 2000 to 4.4% in 2030. Despite medical advances, diabetic foot problems persist as a critical chronic complication, with a 15-25% lifetime risk of foot lesions and an annual incidence of 1 to 4.1%. Osteomyelitis and peripheral arterial disease (PAD) significantly contribute to morbidity, affecting 15% of those with diabetic foot ulcers (DFUs). Diabetes-related vascular issues exacerbate these complications. **Objectives:** 1. Predict osteomyelitis and PAD occurrence in grade 3 and grade 4 DFUs. **Methodology:** This cross-sectional study (2022-2023, Government Medical College, Kozhikode) involves 90 diabetic foot ulcer patients in grades 3 and 4. PCT, ESR, and CRP levels are measured. Follow-up after 3 weeks assesses osteomyelitis and PAD. **Results:** Predictive cut-off values for osteomyelitis are identified: PCT (0.85ng/ml, 100% sensitivity, 92% specificity), CRP (37 mg/ml, 84.6% sensitivity, 83.1% specificity), and ESR (18.5mm/hours, 69.2% sensitivity, 83.1% specificity). For PAD, cut-off values are PCT (0.35ng/ml, 51% sensitivity, 46% specificity), CRP (29 mg/ml, 56% sensitivity, 57% specificity), and ESR (14.5 mm/hr, 49% sensitivity, 55% specificity). **Conclusions:** Elevations in PCT, CRP, and ESR reliably predict osteomyelitis. Early initiation of comprehensive medical and surgical management during hospitalization is crucial for improved patient outcomes with diabetic foot ulcers.

KEYWORDS : Diabetic Foot Ulcer(DFU), Peripheral arterial disease(PAD), Osteomyelitis, Procalcitonin (PCT), Erythrocyte Sedimentation Rate (ESR), and C-reactive Protein (CRP)

INTRODUCTION

Diabetes, a metabolic disorder, triggers severe complications such as cardiovascular disease, renal issues, neuropathy, retinopathy, and vasculopathy, leading to heightened morbidity and mortality (1). Among these, the Diabetic Foot Ulcer (DFU) emerges—a full-thickness wound below the ankle, often induced by peripheral neuropathy or Peripheral arterial disease (PAD) in individuals with diabetes. DFUs are pervasive, impacting over 15% of people with diabetes during their lifetime, elevating the risk of severe foot infections due to neuropathy and vascular dysfunction (2, 3).

Assessing DFU severity and distinguishing between infectious and noninfectious wounds early on is challenging. The PEDIS classification categorizes diabetic foot ulcers as uninfected (grade 1), mild (grade 2), moderate (grade 3), and severe (grade 4) (4). About 15% of individuals with DFUs develop osteomyelitis, often arising from neglected ulcers becoming infected, primarily by *Staphylococcus aureus* (5).

Laboratory tests, including Procalcitonin (PCT), Erythrocyte Sedimentation Rate (ESR), and C-reactive Protein (CRP), serve as acute phase reactants and pro-inflammatory markers. They aid in diagnosing foot ulcer infections and estimating disease severity, particularly in cases involving bacterial infections, osteomyelitis, and PAD (4, 6).

Numerous studies have explored the role of inflammatory markers like ESR, CRP, and PCT in predicting inflammation onset and infection in diabetic wounds, as well as the development of complications such as osteomyelitis and PAD (7). Procalcitonin, a precursor of the calcitonin hormone, is produced in response to the inflammatory cascade, modulated through cytokines associated with sepsis. This study aims to assess the predictive value of PCT, ESR, and CRP in determining the occurrence of osteomyelitis and PAD in grade 3 and grade 4 DFU (4).

By evaluating these markers in grade 3 and grade 4 DFU, this research seeks to enhance our understanding of their diagnostic potential in managing diabetic foot complications. The findings aim to contribute valuable insights that can inform more effective clinical strategies for patients facing these challenging complications.

MATERIALS AND METHODS

Study Design: Cross Sectional Study

Study Population: Patients admitted with DFU in Department of General Surgery, Government Medical College, Kozhikode

Study Duration: One year from the date of clearance from the Institutional Research Committee and Institutional Ethics Committee.

Inclusion Criteria

- Adult (age > 18 years) diabetic patients with grade 3 and 4 ulcers
- Patients with no history of any other inflammatory disease.

Exclusion Criteria

- Patients with diabetic infection age < 18 years.
- Patients already diagnosed with osteomyelitis and PAD.
- Patients in septic shock, unstable hemodynamics .
- Patients already on immunosuppressive therapy

RESULTS

A total of 90 patients with DFU consented and participated in the study. The results and observations are discussed under the following headings;

Part I - Background characteristics of the patients

Part II - Clinical history

Part III - Occurrence of osteomyelitis and PAD.

Part IV - Accuracy of investigations (PCT, CRP and ESR) in prediction of occurrence of osteomyelitis and PAD.

Part I - Background Characteristics Of The Patients

The patient's age varied from 44 to 80 years. The mean age of the participants was 59.16 (8.96) years. Majority of the patients presented with DFU were males (71%). Numbers of male and female patients were 64 and 26 respectively.

Part II - Clinical History

As per the inclusion criteria DFU patients with grade 3 and grade 4 ulcer were selected to the study. More than 60% of participants had grade 3 ulcer. At the time of admission all the patients were screened with X-ray foot and ankle brachial index in order to look for existing osteomyelitis or PAD, and those with presence of these conditions were excluded from the study. Our study included those DFU patients with normal ABI at admission (ABI 0.9-1.29). The mean ABI at admission to hospital was found to have 0.97.

Table 1 - Characteristics Of The Predictive Markers Of Patients (n=90)

Characteristics	PCT	CRP	ESR
Mean ± SD	0.50 ± 0.38	30.85 ± 12.33	5.77 ± 2.90
Median	0.40 (0.2-0.8)	30 (20-38)	15 (10-18)
Maximum	1.5	60	32
Minimum	0.1	10	5

PCT – procalcitonin, CRP – C reactive protein, ESR - Erythrocyte sedimentation rate

Part III - Occurrence Of Osteomyelitis And/Or Pad

A. Occurrence Of Osteomyelitis

Based on an X-ray taken after 3 weeks of admission, it was found that 14% of the patients had features of osteomyelitis. Proportions of development of osteomyelitis were more among those aged <60 years (16.7%), males (40.5%), with DFU grade 3 (16.1%) compared with those with ≥60 years (11.1%) and females (11.5%), with DFU grade 4 (11.8%). But none of these associations were statistically significant (p-value > 0.05).

Part IV - Predictive Accuracy Of PCT, CRP AND ESR

Table 2 - Association Between Predictors And Occurrence Of Osteomyelitis (n=90)

Predictors	Osteomyelitis		Mean difference	P value*
	Absent (Mean ± SD)	Present (Mean ± SD)		
PCT	0.38 ± 0.26	1.19 ± 0.21	0.81	0.01
CRP	28.43 ± 10.82	45.23 ± 11.21	16.80	0.01
ESR	14.06 ± 4.67	21.69 ± 7.79	7.63	0.01

PCT – Procalcitonin, CRP – C reactive protein, ESR – erythrocyte sedimentation rate *Independent t-test

Table 3 - Association Between Predictors And Occurrence Of Pad (n=90)

Predictors	PAD		Mean difference	P value*
	Absent (Mean ± SD)	Present (Mean ± SD)		
PCT	0.53 ± 0.40	0.47 ± 0.36	-0.06	0.457
CRP	28.91 ± 10.21	33.17 ± 14.27	4.25	0.115
ESR	15.47 ± 5.29	14.80 ± 6.48	-0.66	0.594

PCT – Procalcitonin, CRP – C reactive protein, ESR – erythrocyte sedimentation rate *Independent t-test

Predictors For Occurrence Of Osteomyelitis

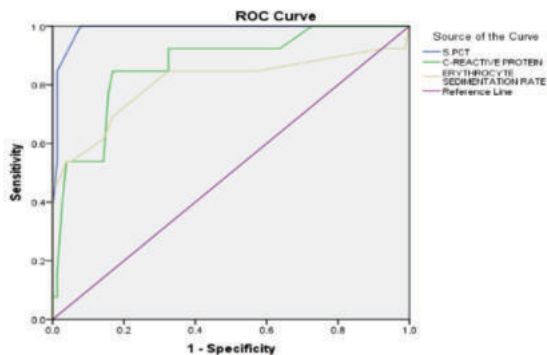


Figure 1 – ROC Curve For PCT, CRP And ESR In Prediction Of Development Of Osteomyelitis In DFU Patients

Among the three predictors (PCT, CRP and ESR), PCT is found to have;

- a) highest AUC
- b) significant p value
- c) highest sensitivity, and
- d) highest specificity.

CRP and ESR also have excellent predictive accuracy (AUC > 0.80, p value < 0.05)

Predictors For Occurrence Of Pad

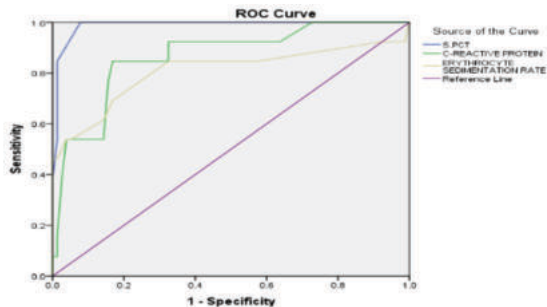


Figure 2 – ROC Curve For PCT, CRP And ESR In Prediction Of

Development Of Pad In DFU Patients

None of the three predictor tests gave a satisfactory AUC.

DISCUSSION

This cross-sectional study, conducted at our institution, aimed to assess inflammatory markers (PCT, ESR, and CRP) in patients with grade 3 and grade 4 DFUs, tracking their subsequent development of osteomyelitis and peripheral arterial disease (PAD).

Ninety participants, comprising 64 males (71.1%) and 26 females (28.9%), were included. The mean age was 59.16 ± 8.96 (50-69), with all patients having HbA1C levels exceeding 6.4, averaging 9.29 ± 1.64.

Of the participants, 56 had grade 3 and 34 had grade 4 ulcers. Mean PCT, CRP, and ESR levels were 0.50, 30.85, and 5.77, respectively.

After three weeks, 13 patients developed osteomyelitis, and 41 developed PAD, representing 14% and 45% of the cohort, respectively. Comparisons with existing studies showed variations in osteomyelitis (36% in Fahimeh et al.) (4) and PAD (24% in Fahimeh et al.) (4). Among those with osteomyelitis, higher mean PCT (1.19 vs. 0.38), CRP (45.23 vs. 28.43), and ESR (21.69 vs. 14.06) levels were observed. For PAD, CRP levels were higher, though not statistically significant (p = 0.115).

PCT emerged as the most accurate predictor of osteomyelitis, with a cutoff value of 0.85 ng/ml, 100% sensitivity, and 92% specificity. CRP and ESR also exhibited excellent predictive accuracy. For predicting PAD, PCT had a cutoff value of 0.35, CRP 29 mg/ml, and ESR 14.5, with varying sensitivity and specificity. Discrepancies with Fahimeh et al. (4) could be attributed to sample size differences.

Despite limitations, such as unknown ulcer and infection durations, this study underscores the significant predictive role of PCT, CRP, and ESR in identifying complications like osteomyelitis and PAD in grade 3 and grade 4 DFUs. These inflammatory markers hold potential as indicators for timely intervention and comprehensive medical and surgical management to prevent these severe consequences.

CONCLUSION

DFUs are among the most common complications of patients who have diabetes mellitus which is not well controlled. DFU can further progress to osteomyelitis and also add to the risk of development of PAD which in turn increases the economic burden and morbidity of the patient. The increase of the three parameters PCT, CRP and ESR can predict the occurrence of osteomyelitis and none of the parameters have an acceptable role in prediction of PAD in patients with grade 3 and grade 4 DFUs. Appropriate medical and surgical management has to be initiated during the initial days of hospitalisation for better outcome of the patients with DFU.

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