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# PROCALCITONIN AS BIOLOGICAL MARKER TO PREDICT THE PROGNOSIS AND FINAL OUTCOME OF DIABETIC FOOT INFECTIONS

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**ABSTRACT: Background:**
**Aim of the study:** To evaluate the prognostic role of procalcitonin (PCT) in patients with diabetic foot infection (DFI) and critical limb ischemia (CLI).
**Materials:** 48 patients diagnosed with diabetic foot Infection and Critical Limb Ischemia (DFI and CLI). All patients were treated using a fixed protocol to salvage limb which included revascularization, wound debridement and antibiotic therapy. Procalcitonin (PCT) values were estimated and the values above 0.5 ng/ml, were considered for admission. Final outcomes of the protocol was categorized as limb salvage (discharge with preserved limb), major amputation (amputation above the ankle), and mortality.
**Results:** 48 patients were included belonging to both genders and aged between 45 years and 75 years. The mean age was 64.2± 06.35 years, 75% were males, and 46/48 (95.83%) of the subjects had type 2 Diabetes. The mean diabetes duration was 23.65±08.15years with a mean HbA1c of 68 ± 12 mmol/mol. 35/48 (72.91%) of patients had limb salvage, 10/48 (20.83%) had major amputation, and 03/48 (06.25%) lost their lives. Patients with positive PCT baseline values in comparison to those with normal values showed a lower rate of limb salvage (30.4 versus 93.6%, p =0 0001), a higher rate of major amputation (13 versus 6.3%, p =0 3), and a higher rate of hospital mortality (56.5 versus 0%, p <0 0001). At the multivariate analysis of independent predictors found at univariate analysis, positive PCT was an independent predictor of major amputation [OR 3.3 (CI 95% 2.0-5.3), p =0 0001] and mortality [OR 4.1 (CI 95% 2.2-8.3), p <0 0001]. Conclusions: Patients with Positive PCT at admission had increased risk of major amputations and mortality in hospital patients with DFI and CLI.

**INTRODUCTION:** Diabetic foot infection (DFI) is a severe complication of diabetic foot ulcers (DFUs) which dramatically increases the risk of limb amputation and mortality [1]. Diagnosis of DFI is usually performed by clinical inspection, and the outcomes of patients with DFI are often related to concomitant comorbidities, mainly peripheral arterial disease [2]. Common inflammatory markers such as c-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cells (WBCs) may be useful for monitoring the response to the treatment but may not specifically assess the severity of DFI and outcomes. Procalcitonin (PCT) is a peptide precursor of the hormone calcitonin which is often undetectable or in very low concentrations (<0.05 ng/ml) in healthy people. In the case of infection, different tissues (kidney, adipose tissue, lung, and liver) secrete

PCT and the blood concentrations can increase regardless of the underlying pathological con- dition [3]. Different studies have highlighted the role of PCT as a diagnostic marker for bacterial infection, which is often more effective than other common markers used in clinical practice, such as CRP, ESR, and WBC, and may be more reliable than some experimental markers such as interleukin- 6 (IL-6) or interleukin-8 (IL-8) [4]. Furthermore, PCT is a prognostic marker of severity linked to mortality rates in infectious processes [5, 6]. Several observational studies have also found that PCT is a suitable marker to distinguish bacterial infections in DFUs [7–9]. Despite this fact, the prognostic role of PCT in DFI has never been clearly evaluated. The aim of this study is to establish the prognostic role of PCT in hospital diabetic patients with critical limb ischemia (CLI) and DFI.

## MATERIALS

The study was conducted at a Tertiary care General Hospital attached to Kannur Medical College between September 2017 December 2018 and 48 patients diagnosed with CLI and moderate-to-severe DFI attended the Department of General Medicine. An Institution ethics committee approval was obtained before commencing he study. An ethics committee approved proforma was used for the study.

**Inclusion Criteria:** Patients aged between 45 and 75 years were included. Patients of both the genders were included. Patients with CLI and moderate-to-severe DFI were included. Patients willing to participate in the Hospital protocol for preset limb salvage including revascularization, wound debridement, antibiotic therapy, and offloading were included.

**Exclusion Criteria:** Patients aged below 45 years and above 75 years were excluded. Patients not willing to participate in the study were not included. Patients with risk factors of malignant hypertension, auto-immune diseases and Immuno-deficiency disorders were excluded. The CLI was defined according to the combination of clinical findings and TcPO2 (<30 mmHg) or ankle-brachial index (<0.9) was used. Revascularization was performed in all cases by endovascular approach. Moderate and severe infections were defined according to the Infectious Disease Society of America (IDSA) and International Working Group on Diabetic Foot (IWGDF) [10]. Moderate infection was identified according to the involvement of structures deeper than the skin and subcutaneous tissues in addition to the presence of Erythema of more than 2 cm but without signs of systemic inflammatory response. Severe infection was identified when the local infection as described above is associated with at least 2 signs of systemic inflammatory response: temperature of >38°C or <36°C, heart rate of >90 beats/min, respiratory rate of >20 breaths/min or $PaCO_2$ of <32 mmHg, WBCs count of >2000 or <4000 cells/µl, or 10% immature [band] forms. Early debridement was performed in the case of abscess, compartmental syndrome, wet gangrene, and necrotizing fasciitis to avoid the progression of the infectious process; otherwise, curative surgery was performed after revascularization. Antibiotic treatment started as empirical broad-spectrum therapy and was later driven by culture, if required. Close monitoring of renal function, glycemic levels, electrolyte balance, anemia, and pain was performed. Demographic data and co-morbidities have been reported. Hypertension was considered when blood pressure values were higher than 140/90 mmHg or there was a need for anti-hypertensive therapy; dyslipidemia was classified as LDL of >70 mg/dl or a need for statin therapy [10]; ischemic heart disease was considered in the case of previous coronary acute syndrome, coronary revascularization, or electrocardiogram abnormalities [11 to13]; carotid artery disease was considered in the case of occlusion or stenosis of >50% or in the case of previous carotid revascularization. Dialysis was considered when chronic renal replacement therapy was required. Inflammatory markers, including PCT, were evaluated for all patients at admission. Positive values of PCT were considered if greater than 0.5 ng/ml. Hospital outcomes were determined by limb salvage (discharge with preserved limb), major amputation (amputation above the ankle), and mortality. Statistical analysis was performed by SAS (JMP12; SAS Institute, Cary, NC) for the personal computer. Data are expressed as means ± SD. Uni-variable logistic regression analyses were performed for all potential predictor variables with the outcome of interest

(limb salvage, major amputation, and mortality) with values presented as uni-variable odds ratios (ORs) along with the respective 95% CI. Then, all potential predictors were entered simultaneously in a multivariate logistic regression model. These models yielded a set of variables that best predict the outcome. p <0 05 was considered statistically significant.

**RESULTS:** The demographic data of the 48 patients was tabulated in **Table 1.**

| Observation | Number | Percentage | P value |
|---|---|---|---|
| **Age**<br>45 to 55 Yrs<br>55 to 65 Yrs<br>65 to 75 Yrs | <br>11<br>24<br>13 | <br>22.91<br>50<br>27.08 | 0.143 |
| **Gender**<br>Male<br>Female | <br>36<br>12 | <br>75<br>25 | 0.215 |
| **Type of Diabetes**<br>Type 2 | 46 | 95.83 | 0.01 |
| Duration of Diabetes (Mean duration) | 23.65±08 | -- | 0.01 |
| HbA1c (mmol/mol | 66±13 (8.5±3.1) | -- | 0.001 |
| Hypertension | 33 | 68.75 | 0.01 |
| Dyslipedemia | 30 | 62.5 | 0.01 |
| Current smokers | 18 | 37.5 | 0.01 |
| Heart Failure | 22 | 45.83 | 01.33 |
| CAD | 11 | 22.91 | 0.163 |
| IHD | 36 | 68.75 | 0.01 |
| ESRD (dialysis) | 17 | 35.41 | 0.122 |
| (PCT)-Procalcitonin -ng/ml | 1.5±0.4 | -- | 0.001 |
| ESR mm/Hr | 116±11 | -- | 0.01 |
| CRP mg/dl | 83.5±32.6 | -- | 0.01 |
| WBC ($X10^{8/ML}$) | 11.5±2.9 | -- | 0.154 |
| Fibrinogen | 441±143 | -- | 0.01 |
| Wound parameters | 39 | 81.25 | 0.01 |
| Dimensions > $5Cm^2$ | 41 | 85.41 | 0.001 |
| $TcPo_2$ | 24.10±6.8 | 22 4±7 9 | 0.01 |

**Table 2: Showing the Demographic details of the study. (n-48)**
**(IHD: Ischemic heart disease; CAD: carotid artery disease; ESRD: end-stage renal disease; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; $TcPO_2$: transcutaneous foot oximetry; WBC: white blood cells; PTA: percutaneous transluminal angioplasty.)**

The final outcome of the present study showed that 35/48 (72.91%) of patients had limb salvage, 10/48 (20.83%) had major amputation, and 03/48 (06.25%) lost their lives. 01/03 patient died from sepsis, 2/03 from acute coronary syndrome. 30/48 (62.5%) patients had a positive PCT values at the time of enrolling them to the study. Among these 18/30 (60%) had moderate infection, 12 /30 (40%) had severe infection according to IDSA classification. The mean value of PCT at the time of admission was 4.9±1.30 as against the normal values of 0.02±0.01 ng/ml. The patients with positive PCT reported a higher rate of ESRD and heart failure in comparison to patients with normal values of PCT. **(Table 2)** Patients with positive PCT baseline values in comparison to those with normal values showed a lower rate of limb salvage (37.5 versus 62.5%, p =0 001), higher rate of major amputation: 10/48 (20.83%) versus 05.3%, p =0.01), and a higher rate of hospital mortality (56.5 versus 0%, p <0

0001). There were no significant divergences in outcomes according to the values of other common inflammatory markers, such as WBC, CRP, ESR, and fibrinogen, except for the higher values of CRP in the deceased patients in comparison with the survivors. At the multivariate analysis of independent predictors found at univariate analysis, revascularization failure [OR 2.8 (CI 95% 1.9-3.1), p =0 002] and positive PCT [3.3 (CI 95% 2.0-5.3), p =0 0001] were independent predictors of in-hospital major amputation. Mortality: At the multivariate analysis of independent predictors found at univariate analysis, positive PCT+ [OR 4.1 (CI 95% 2.2-8.3), p <0 0001] and heart failure [1.8 (CI: 95%1.05-5.5), p =0 003] were independent predictors of in-hospital mortality. WBC, ESR, CRP, and fibrinogen were not independent predictors of outcome.

| Variables | Positive PCT | Normal PCT | P values |
|---|---|---|---|
| Moderate Infection | 18- 60% | -- | |
| Severe Infection | 12- 40% | -- | |
| ESRD- 17 | 10-58.82% | 07-41.7% | 0.001 |
| IHD- 36 | 26-72.72% | 10-27.27% | 0.001 |
| 01Heart Failure- 22 | 12-54.54% | 10-45.45% | 0.01 |

**Table 2: Showing the Positivity of procalcitonin according to the degree of infection and co-morbidities. (n- 48).**

## DISCUSSION

The present study was conducted with an aim to evaluate the prognostic role of procalcitonin (PCT) in patients with diabetic foot infection (DFI) and critical limb ischemia (CLI). While several studies have highlighted the potential of PCT as a diagnostic marker for diabetic foot infection (DFI) [9], only two have examined its link to amputation in DFI patients [14, 15]. In the present study an attempt was made for the first time to assess the prognostic value of PCT in hospitalized patients with DFI and critical limb ischemia (CLI). The observations showed that elevated PCT levels were observed in a significant subset of patients, regardless of the infection's severity as classified by IDSA guidelines. However, those with elevated PCT at admission experienced worse outcomes, including higher rates of amputation and mortality, compared to patients with normal PCT levels. In contrast, commonly used inflammatory markers such as WBC, CRP, ESR, and fibrinogen did not correlate with patient outcomes in this cohort. Additionally, PCT emerged as an independent predictor of both amputation and mortality, alongside factors like failed revascularization and heart failure. While revascularization failure is a well-established predictor of major amputation [14], the potential role of PCT in predicting lower limb amputation has been explored with mixed findings. In a small case-control pilot study with 27 patients, Karakas et al. did not find significantly higher PCT levels in amputees compared to non-amputees [15]. However, a larger case-control study of 156 DFI patients requiring surgical intervention, conducted by Reiner et al., found that PCT levels were significantly higher at admission (median 1.7 ng/ml) in patients who eventually underwent below-the-knee or above-the-knee amputation, compared to those whose limbs were salvaged (median 0.105 ng/ml) [16]. In this study, 10/48 (20.83%) of patients with elevated PCT levels at admission underwent major amputation due to infection progression and persistent limb ischemia after failed revascularization. Elevated PCT levels may indicate a more aggressive infection, which becomes more difficult to treat when compounded by poor blood flow. PCT is a well-established prognostic marker for mortality, commonly used to assess the severity of infection, particularly in sepsis cases in acute care settings [5, 6, 17]. Heart failure is another recognized predictor of mortality in patients with diabetic foot syndrome [18], though the relationship between PCT and mortality in DFI and CLI patients has not been previously explored. In this study, patients with elevated PCT at admission experienced a significantly higher mortality rate (approximately 56%), with most deaths linked to septic shock. The patients in the present study were critically ill, underscoring the severity of their conditions. The patients in this study, at the highest risk for adverse outcomes, were referred from the emergency department, often had multiple co-morbidities, and some already showed signs of sepsis upon admission. It's important to note,

however, that not all patients with elevated PCT were septic at the time of referral. In some cases, PCT levels were elevated in patients with moderate infection, as well as in those with severe infection, regardless of the infection's grade. Moreover, the severity of the infection itself did not emerge as an independent predictor of outcome. (19, 20) Regarding the major co-morbidities among patients with elevated PCT, a high proportion had end-stage renal disease (ESRD) or ischemic heart disease (IHD). Specifically, 35.41% of these patients were on dialysis, and 45.83% had concurrent heart failure. This suggests that severe co-morbidities like renal and heart failure could predispose patients with infected diabetic foot ulcers (DFUs) to a stronger systemic inflammatory response. PCT may serve as a marker of an intense acute inflammatory response, reflecting overall dys-regulation, even in patients without sepsis, such as those with moderate DFI. Recent studies have shown that PCT levels are not solely linked to infection but are also significantly associated with organ dysfunction. Dysfunction and tissue injury as described after cardiac surgery in patients with acute myocardial ischemia [19, 20].

**CONCLUSIONS:** This study was an attempt that was conducted after reviewing the literature, to examine the role of PCT as an outcome marker in hospitalized patients with ischemic-infected diabetic foot. Based on our findings, PCT may serve as a predictor of mortality in hospital patients with critical limb ischemia (CLI) and moderate-to-severe infection. Its prognostic value should be considered when assessing these patients, regardless of the infection's clinical severity. PCT could also be useful in the early identification of a systemic inflammatory response, even in non-septic patients. It may help pinpoint high-risk individuals, even in the absence of obvious clinical signs, and guide clinicians in making important decisions, such as whether intensive care is needed, whether to reinforce antibiotic therapy, and how closely to monitor vital signs, hemodynamic parameters, and laboratory values. However, PCT should always be interpreted in conjunction with the patient's medical history and clinical assessment.

**STUDY LIMITATIONS**: This is a retrospective study conducted at a single center. Diabetic foot syndrome (DFS) is a complex condition, and other factors may also influence the final outcomes. Additional studies are needed to determine whether elevated PCT levels in patients with diabetic foot infection (DFI) are associated with concurrent co-morbidities and whether early PCT analysis could lead to improved patient outcomes.

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