

Role of Procalcitonin as a Predictor of Clinical Outcome in Acute Diabetic Foot Infections: A Prospective Study

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Abstract

Background: Prediction of outcome in diabetic foot infection (DFI) remains difficult due to lack of active signs of infection, and apparently normal white blood cell (WBC) count. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been studied previously in this regard and were not useful. Hence, we evaluated procalcitonin (PCT) as a prognostic marker in this study. **Objectives:** We aimed to study the role of PCT, CRP, and ESR levels in predicting clinical outcome of acute DFI. **Materials and Methods:** A total of 250 subjects (197 men, 53 women) with acute DFI were enrolled. WBC count, ESR, CRP, and PCT were done for all subjects at admission after obtaining informed consent. Subjects were managed according to hospital protocol and followed up for 1 month. Clinical outcome was assessed based on mobility and morbidity status of the subject. **Results:** Old age, anemia, hyponatremia, hypoalbuminemia, and elevated serum creatinine were risk factors for poor outcome. Presence of cardiac failure, diabetic retinopathy, peripheral vascular disease, previous amputations, and positive bone culture had negative influence on clinical outcome. Elevated WBC count, ESR, CRP, and serum PCT were significantly associated with bad outcome. Elevated PCT (>2 ng/ml) [odds ratio (OR) (95% confidence interval (CI)), 2.03 (1.13–5.19), $P < 0.001$], gangrene [OR (95% CI), 2.2 (1.02–4.73), $P = 0.04$], and sepsis [OR (95% CI), 10.101 (4.34–23.25), $P < 0.001$] were good predictors of clinical outcome in acute DFI. **Conclusion:** PCT proved to be a reliable marker of acute DFI and good predictor of clinical outcome than existing markers WBC count, ESR, and CRP. Hence it should be useful for clinicians while managing acute DFI.

Keywords: C-reactive protein, diabetic foot infection, erythrocyte sedimentation rate, procalcitonin

INTRODUCTION

It has been projected that diabetes will affect around 57.2 million people in India by 2025 based on the calculation from the World Health Organization (WHO) global estimate for prevalence of diabetes in 1993.^[1] Diabetic foot infection (DFI) is one of the life-threatening complications of diabetes. About 2–3% of those with diabetes develop foot ulcer every year requiring prolonged hospitalization.^[2] Diabetes alone accounts for 60% of nontraumatic lower extremity amputations due to DFI and ensuing osteomyelitis.^[3,4] Diabetes affects multiple systems compromising local and systemic response to infection, potentially masking typical clinical features, and thereby delaying or hindering diagnosis.^[5] Hence use of traditional blood counts is not much useful in diagnosing or classifying acute DFI.^[6] This led to the usage of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as alternative diagnostic markers. Both these markers have shown

to be useful in diagnosing underlying infection, particularly osteomyelitis,^[7] and prediction of possible amputation^[8] to some extent. But the reliability of these markers remains questionable.

Procalcitonin (PCT), a peptide precursor of calcitonin has been used to detect bacterial infection with high sensitivity. PCT level rises in response to proinflammatory stimulus, exclusively of bacterial origin and has been used extensively in diagnosing surgical infections. It has also been used as a diagnostic marker in acute DFI in some studies.^[4,9,10] But its

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use in predicting the outcome of acute DFI in comparison with ESR and/or CRP is not well studied. Hence this study was designed to compare the existing parameters, ESR and CRP with PCT levels in predicting the outcome of acute DFI.

MATERIALS AND METHODS

Study subjects

This prospective study included 250 subjects with acute DFI presenting to Department of Endocrinology and Podiatry between January 2013 and December 2014. Inclusion criteria were (1) clinical diagnosis of acute DFI according to Infectious Disease Society of America 2012 guidelines^[11] and classification based on the system developed by Infectious Disease Society of America-International Working Group on the Diabetic Foot^[12] (IDSA-IWGDF) (abbreviated with the acronym PEDIS) and (2) onset of DFI <2 weeks. Individuals with type 1 diabetes, inflammatory diseases, and chronic bacterial infections were excluded.

Methods

This study was approved by Institutional Review Board of our Institute. Sample size was determined based on the pilot study done in the same institution with 30 consecutive subjects in which 24 had good outcome and six had bad outcome. Based on the results, mean and standard deviation of both variables (ESR and CRP) in two groups (good and bad outcomes) and with 99% confidence and 90% power, minimum sample size comes to 50 in each group. However, as the proportion of bad to good outcome is 1:4, 250 cases (200 subjects with good outcome and 50 subjects with bad outcome) were included.

After obtaining informed consent, patients were subjected to clinical examination and biochemical, radiological, and microbiological evaluation before the first dose of antibiotic at our hospital. Venous blood sample was obtained to measure fasting plasma glucose, 2 h postprandial plasma glucose, HbA1c, blood urea, serum creatinine, liver function tests, complete blood count (CBC), ESR, CRP, serum PCT, fasting lipid profile, and serum albumin. Urine microscopy examination, radiograph of the chest, affected foot and deep tissue culture from the infected site were also done. Urine microscopy and chest X-ray were done to rule out coexisting infection, which could falsely elevate PCT levels.

Plasma glucose and hemoglobin A1c (HbA1c) were estimated by hexokinase and HPLC (NGSP and DCCT – standardized method), respectively. CBC was performed by electrical impedance method. ESR and CRP were done by Seditainer method and immunoturbidometric method, respectively. PCT was measured by electro chemiluminescence immunoassay method (B.R.A.H.M.S ElecSys PCT kit, Hennigsdorf, Germany) using Cobas immunoassay analyzer (Roche Diagnostics) with a functional sensitivity of 0.06 ng/ml and analytical sensitivity of <0.02 ng/ml. The measuring range was 0.02–100 ng/ml with a coefficient of variation (CV) of 3.7%.

Subjects were managed as per the working protocol of the Department of Endocrinology and Podiatry. Clinical outcome was assessed at 1 month following therapy under four categories:

1. Completely healed wound
2. Minor debridement/amputation (debridement of necrotic tissue/amputation of one or more digits)
3. Major amputation (lower extremity amputation performed below/above knee)
4. Death.

Categories 1 and 2 were considered as good outcomes as the patient would still be ambulant, whereas categories 3 and 4 were considered as bad outcomes.

Definition of variables

PEDIS 3 (limb-threatening) was defined as infection in a patient who is systemically well and metabolically stable but has >1 of the following characteristics:

- Cellulitis extending >2 cm
- Lymphangitic streaking
- Spread beneath the superficial fascia
- Deep tissue abscess
- Gangrene
- Involvement of muscle, tendon, joint or bone AND/OR ischemia [ankle-brachial index (ABI) <0.8].

PEDIS 4 (life-threatening) was defined as infection in a patient with systemic toxicity or metabolic instability:

- Fever/Chills
- Tachycardia (HR >100/min)
- Hypotension (systolic BP <100 mmHg)
- Confusion
- Leukocytosis/Leukopenia
- Acidosis
- Severe hyperglycemia (RBS >500 mg/dl)
- Azotemia.

Sepsis: Definitive diagnosis of sepsis required clinical identification of infection in a patient who also meets the clinical criteria for the systemic inflammatory response syndrome (SIRS). According to a revised consensus conference definition in 2001, SIRS is defined by the presence of two or more criteria from a collection of clinical signs and laboratory investigations as follows:

- Temperature >38.3°C (101°F) or < 36.0°C (96.8°F)
- Tachycardia >90 beats/min
- Tachypnoea >20 breaths/min
- PCO₂ <32 mmHg
- Hyperglycemia (blood glucose >120 mg/dl) in the absence of diabetes mellitus
- Acutely altered mental status
- WBC count >12 × 10⁹/l or <4 × 10⁹/l or normal WBC count with >10% immature forms.

Coronary artery disease (CAD): Presence of ECG changes or echo abnormalities or cardiac enzyme elevation at the time of hospitalization.

Chronic kidney disease (CKD): Presence of elevated serum creatinine or increased cortical echotexture of kidneys in ultrasound or on maintenance dialysis at the time of hospitalization.

Chronic liver disease (CLD): Presence of elevated SGOT and SGPT with A/G reversal or ultrasound features suggestive of CLD at the time of hospitalization.

Peripheral occlusive vascular disease (POVD): Presence of ABI <0.9 or lesser than triphasic flow in the peripheral vessels with handheld Doppler at the time of hospitalization.

Statistical analysis

Statistical analysis was done using IBM SPSS Statistics 20 Windows (SPSS Inc., Chicago, USA). Student's *t*-test was used to assess statistical significance of the difference in mean values of measurable variables between the good and bad outcome groups. Correlation of clinical outcome with demographic, clinical, and biochemical parameters were determined using Chi-square test and odds ratio with corresponding 95% confidence interval (CI) were computed. A receiver-operating characteristic (ROC) analysis and the area under the ROC curve (AUC) were calculated to estimate accuracy of PCT in predicting clinical outcome, as well as its specificity and sensitivity using the best cut-off value. $P < 0.05$ was considered statistically significant. Stepwise multivariate logistic regression analysis was also done including all variables, which were found to be statistically significant ($P < 0.05$) in univariate analysis.

RESULTS

Descriptive statistics

A total of 250 patients with acute DFI were included in the study (mean age 61.63 ± 10.18 years). Majority of study population were males (78.8%). Duration of diabetes in good and bad outcome groups was 15.06 ± 7.05 and 16.56 ± 6.26 years, respectively. Prevalence of comorbidities include hypertension (85.6%), dyslipidemia (71.2%), CAD (46.4%), CKD (25.2%), history of stroke (6%), and CLD (9.6%) in the study cohort. Peripheral neuropathy and POVD were observed in 96.8 and 90.8%, respectively. Approximately 40.8% were former smokers (quit smoking at the time of the study) and only 1.2% of the study population were current smokers. About half of the study population had fever at presentation. DFI was most commonly located in right forefoot (30.8%) and bilateral foot infection was documented in 3.2%. 25.6% had previous toe amputations and 37.2% had gangrene at presentation. Osteomyelitis could be identified in 42% with foot radiograph and in 71.6% (111 out of 155 subjects in whom it was done) with positive bone culture. Life-threatening infection occurred in 43 (17.2%) patients, and 147 patients (58.8%) had sepsis. Distribution of subjects according to PEDIS classification are PEDIS 2 (134 subjects, 53.6%), PEDIS 3 (110 subjects, 44%), and PEDIS 4 (6 subjects, 2.4%), and according to University of Texas classification 2B (1 subject, 0.4%), 2C (52 subjects,

20.8%), 2D (96 subjects, 38.4%), 3B (2 subjects, 0.8%), 3C (29 subjects, 11.6%), and 3D (58 subjects, 23.2%). Baseline biochemical parameters of the study population are summarized in Table 1.

Clinical outcome

Correlation between clinical parameters and clinical outcome of acute DFI is shown in Table 2. Comparison between WBC count, ESR, CRP, and PCT in predicting clinical outcome of acute DFI is shown in Table 3. Multivariate logistic regression analysis of statistically significant parameters in univariate analysis showed that presence of sepsis, gangrene, and elevated PCT levels were good predictors of bad outcome in acute DFI [Figure 1]. ROC analysis showed a good predictive value for PCT in prognosticating clinical outcome of patients with acute DFI (AUC 0.807, $P < 0.001$) with 80% sensitivity and 75% specificity for a value of 0.583 ng/ml [Figure 2]. Comparison of PCT with CRP in predicting clinical outcome showed that an increase in 1 ng/ml of PCT had a 38.4% (95% CI 20.7–58.6%) increase in the odds of having bad outcome by binary logistic regression analysis.

DISCUSSION

In our study, WBC count, ESR, CRP, and PCT levels were significantly higher in the bad outcome group alike the existing studies.^[8,9,13] PCT showed good predictive value for bad outcomes with 80% sensitivity and 75% specificity for a

Table 1: Biochemical parameters of study population (n=250)

Variables	Good outcome (n=200)		Bad outcome (n=50)		P
	Mean	SD	Mean	SD	
WBC (ku/ml)	12.7	5.84	18.22	8.74	<0.001
Polymorphs (%)	70.1	12.4	79.41	10.75	<0.001
Lymphocytes (%)	18.63	9.37	12.33	8.25	<0.001
Hemoglobin (g/dl)	10.84	1.7	10.27	1.47	0.03
Platelets (ku/ml)	322.45	139.6	366.48	171.08	0.097
ESR (mm/h)	54.7	18.44	56.23	17.42	0.58
CRP (mg/l)	98.68	90.04	150.57	90.59	<0.001
Procalcitonin (ng/ml)	0.77	1.69	3.14	3.87	<0.001
FPG (mg/dl)	153.83	66.71	150.54	68.19	0.75
PPG (mg/dl)	214.45	72.95	221.35	92.31	0.57
HbA1c (%)	9.24	2.04	9.11	1.77	0.66
Blood urea (mg/dl)	39.27	27.19	54.07	47	0.03
Serum creatinine (mg/dl)	1.6	1.13	1.95	1.83	0.2
AST (IU/l)	29.81	21.2	45.98	32.96	0.002
ALT (IU/l)	29.81	22.89	44.97	43.08	0.02
Serum albumin (g/dl)	3.13	0.53	2.69	0.53	<0.001
Serum globulin (g/dl)	3.58	0.52	3.9	0.7	0.003
Albumin/globulin ratio	0.89	0.22	0.7	0.17	<0.001
Serum sodium (meq/l)	132.79	5.36	129.98	5.28	0.001

DM=Diabetes mellitus, WBC=White blood cell count, ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein, FPG=Fasting plasma glucose, PPG=Postprandial glucose, HbA1c=Glycosylated hemoglobin, AST=Aspartate transaminase, ALT=Alanine transaminase

Table 2: Correlation between clinical parameters and clinical outcome of acute diabetic foot infections

Variables	Category		% of good outcome	OR	95% CI		P
					Upper	Lower	
Age (years)	<59	n=108	86	2.02	1.042	3.946	0.035
	≥60	n=142	75.4				
Systemic hypertension	Yes	n=214	78	3.096	0.909	10.543	0.05
	No	n=36	91.7				
Coronary artery disease	Yes	n=116	74.1	1.988	1.058	3.738	0.03
	No	n=134	85.1				
Diabetic retinopathy	NPDR	n=155	74.8	1.547	0.551	4.345	0.05
	PDR	n=28	82.1	3.586	1.040	12.365	
	No	n=35	91.4	3.250	0.938	11.262	
Anemia	Yes	n=51	70.6	1.95	0.965	3.948	0.06
	No	n=199	82.4				
Dorsalis pedis pulse	Absent + Faint	n=62	59.7	4.195	2.156	8.164	<0.001
	Monophasic	n=173	86.1	9.459	1.169	76.575	
	Biphasic	n=15	93.3				
Posterior tibial pulse	Absent + Faint	n=51	58.8	4.144	2.057	8.349	<0.001
	Monophasic	n=173	85.5	3.85	1.157	12.814	
	Biphasic	n=26	84.6				
Popliteal pulse	Absent+Faint	n=5	40	5.478	0.863	34.76	0.057
	Monophasic	n=107	78.5	7.125	1.129	44.977	
	Biphasic	n=138	82.6				
Cardiac failure	Yes	n=12	41.7	6.35	1.923	20.957	0.001
	No	n=238	81.9				
Gangrene	Yes	n=93	67.7	3.26	1.721	6.184	<0.001
	No	n=157	87.3				
Loss of toes	Yes	n=64	59.4	4.618	2.392	8.915	<0.001
	No	n=186	87.1				
Life-threatening infection (PEDIS 3)	Yes	n=43	32.6	18.347	8.399	40.076	<0.001
	No	n=207	89.9				
Sepsis	Yes	n=43	32.6	18.347	8.399	40.076	<0.001
	No	n=207	89.9				
Bone culture	Positive	n=111	54.5	5.233	1.916	14.29	<0.001
	Negative	n=44	77.5				
Serum albumin (g/dl)	<2.5	n=41	65.9	2.492	1.19	5.215	0.013
	≥2.6	n=209	82.8				
Serum sodium (meq/l)	<130	n=76	64.5	3.618	1.902	6.88	<0.001
	≥131	n=174	86.8				

NPDR=Nonproliferative diabetic retinopathy, PDR=Proliferative diabetic retinopathy, OR=Odds ratio, %=Percentage

value of 0.583 ng/ml, which is similar to the observation in the Korean study.^[14] An increase in PCT by 1 ng/ml is associated with 38.4% increase in the likelihood of having a bad outcome. PCT (>2 ng/ml), gangrene, and sepsis are good predictors of clinical outcome in acute DFI.

Red blood cell count, hemoglobin, serum albumin, and sodium were lower in bad outcome group comparable with the previous studies.^[8,15] Other observations include higher blood urea, serum creatinine, AST, ALT, and INR in bad outcome group, which were not mentioned in the earlier studies. Fasting blood sugar (FBS), postprandial blood sugar, and HbA1c were comparable in both groups, unlike former studies where FBS and HbA1c were significantly higher in the poor outcome group.^[16] Younger patients had better outcome and no difference in gender was observed, unlike in

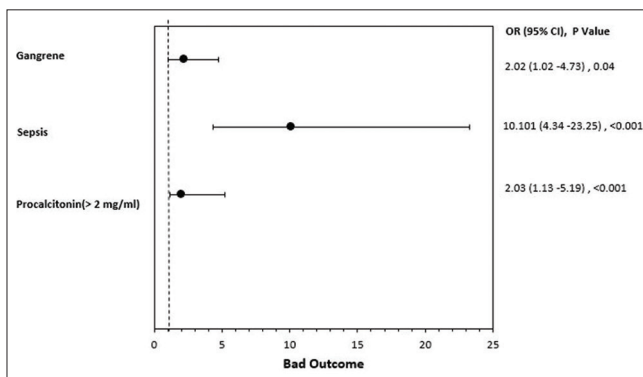
earlier studies where male sex was shown to be a risk factor for bad outcome.^[17] Hypertension was associated with lesser chances of good outcome. This could probably be attributed to endothelial dysfunction following shear stress on blood vessels that could result in poor tissue repair. In addition, those who had CAD had poor outcome as observed in Turkish cohort study.^[8] This shows that the macrovascular complications of diabetes begin in all blood vessels simultaneously, including coronaries and femoral vessels. However, presence of stroke, CLD, and CKD did not show any difference in outcome, which was in contrast to earlier studies.^[16]

Absence of POVD implied good outcome that could be partly due to referral bias to our tertiary center and lesser subjects in non-POVD group. Diabetic retinopathy showed significant correlation with outcome of acute DFI in this study similar

Table 3: Comparison between WBC count, ESR, CRP, and PCT in predicting the clinical outcome of acute DFIs

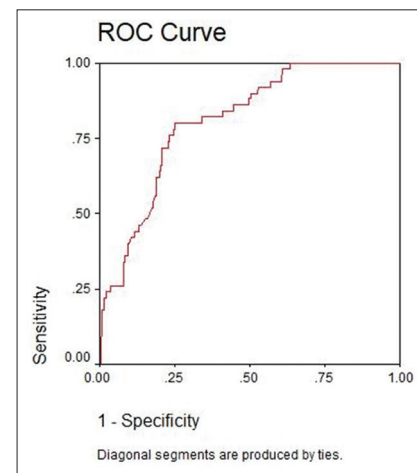
Variable	Category		% of good outcome	% of bad outcome	OR	95% CI		P
						Lower	Upper	
WBC (ku/ml)	<11.3	n=109	92.7	7.3	5.35	2.394	11.983	<0.001
	≥11.4	n=141	70.2	29.8				
ESR (mm/h)	<39	n=42	81	19	1.044	0.449	2.426	0.92
	≥40	n=208	79.8	20.2				
CRP (mg/l)	<1	n=2	100	0	–			0.47
	≥1.1	n=248	79.8	20.2				
PCT (ng/ml)	<0.046	n=15	100	0	2.03	1.130	5.190	<0.001
	0.047-1.9	n=198	83.8	16.2				
	>2	n=37	51.4	48.6				

WBC=White blood cell count, ESR=Erythrocyte sedimentation rate, CRP=C-reactive protein, OR=Odds ratio, %=percentage

**Figure 1:** Factors predicting clinical outcome in acute DFIs by forest plot analysis

to Wisconsin epidemiologic study of diabetic retinopathy, where retinopathy showed significant correlation with 14-year cumulative incidence of amputation.^[17] Absence of peripheral neuropathy showed a relatively better chance of good outcome supporting the Seattle diabetic foot study.^[18] Smoking did not show any difference in outcome that was quite different from many existing studies^[8,17] but alike a few.^[19]

Presence of gangrene and prior loss of toes at admission showed significant reduction in favorable outcome. This shows that preexisting diffuse vascular disease and loss of sensation due to neuropathy put rest of the toes or even the limb at risk for amputation. Presence of necrosis and slough in the wound showed less probability of good outcome. Tissue ischemia, persistence of underlying infection, and lesser concentration of antibiotics could be the reason. Patients presenting with cardiac failure showed lower frequency of good outcome as observed in various studies.^[19] Patients who had life-threatening infection (PEDIS 3) and sepsis at admission had significantly lesser frequency of good outcome. Usage of culture-specific antibiotics did not show correlation with outcome possibly due to the polyclonality of microorganisms commonly seen in DFI and lack of anaerobic culture. Use of low molecular weight heparin was associated with decrease in good outcome reflecting presence of underlying POVD and requirement for revascularization. Positive bone culture had more bad outcomes, same as the observation in the Turkish cohort study.^[8]

**Figure 2:** PCT predicted clinical outcome in acute DFI (AUC 0.807, $P < 0.001$) with 80% sensitivity and 75% specificity for a value of 0.583 ng/ml

Strengths of our study include larger number of patients who underwent thorough and uniform baseline foot examination by experienced podiatrists. We also used standard definitions for diagnosing and classifying foot infections using both PEDIS and University of Texas classification. There are some limitations. First, this was a short-term follow-up study and so outcome could have changed later. Second, biochemical parameters were measured only once due to logistic reasons. Third, we had lesser number of subjects in bad outcome group which could have interfered in certain observations, and so we recommend larger controlled studies to confirm these observations. Finally, reliability of PCT level is doubtful in the presence of concomitant infection. PCT measurement may cost more, but it has been shown to be cost-effective when duration of hospital stay, usage of antibiotics and time taken to get back to work are considered.^[20,21]

CONCLUSION

PCT appears to be a reliable marker of acute DFI and a better predictor of clinical outcome than the existing markers, ESR, CRP, and WBC count. Along with the clinical prognosis predictors such as gangrene and sepsis, elevated PCT should be useful for clinicians in prognosticating clinical outcome,

decision-making as well as managing patients with acute DFIs.

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Conflicts of interest

There are no conflicts of interest.

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