The Egyptian Journal of Hospital Medicine (July 2024) Vol. 96, Page 2547-2552

Procalcitonin/Lactate Ratio as a Diagnostic Marker for Osteomyelitis in Patients with Diabetic Foot Ulcers

Khaled Ahmed El-Banna [1], Fawzy Abd El-Fattah El-Messallamy [1], Jehan Saeed AbdoSoliman [1], Nermin Saad Ghanim[1], Ahmed Atef Zaki El-naggar [1], Ahmed Sallam Soliman [2], Noha Usama Khalil [1]

[1] Internal Medicine Department, [2] Clinical Pathology Department, Faculty of Medicine, Zagazig University, Egypt

Corresponding author: Khaled Ahmed El-Banna, **Email:** khaledelbanna76@gmail.com, **Mobile:** +201118262030

ABSTRACT

Background: Diabetes patients are more likely to experience foot infections, which are extremely morbid and raise the possibility of lower limb amputation. The clinical symptoms and indications of local inflammation are used to diagnose diabetic foot infections (DFI).

Objective: This study aimed to evaluate procalcitonin/Lactate ratio as a diagnostic marker for osteomyelitis and soft tissue infection in diabetic foot ulcers.

Patients and methods: This case-control study was carried out on 112 diabetic patients attending to Diabetic Foot Outpatient Clinic, Zagazig University. Patients were divided into 4 groups: Group (1) included patients with T2DM without foot complications, group (2) patients with non-infected diabetic foot ulcer (NIDFU), group (3) that included infected diabetic foot without osteomyelitis and group (4) Infected diabetic foot with osteomyelitis. Full clinical examination, routine and metabolic investigations were done. Procalcitonin, lactic acid level and procalcitonin/lactate ratio were measured for all subjects. In addition, MRI on bone of infected diabetic foot groups was done.

Results: A statistically significant increase in serum procalcitonin, lactic acid level and procalcitonin/lactate ratio were found in infected diabetic foot with osteomyelitis than those without osteomyelitis and those of diabetic foot ulcer without infection and those without foot complications. Also, there was significant increase in those without osteomyelitis than in those of diabetic foot ulcer without infection and those without foot complications. Elevated WBCs, T. cholesterol and serum triglyceride were independent predictors of elevated procalcitonin (PCT)/lactate ratio. Procalcitonin/lactate ratio at cut-off value of ≥ 0.31 could be a marker for early detection of infected diabetic foot ulcers without osteomyelitis with 95.9 % sensitivity and 92.4% specificity. Also, cut-off value of ≥ 2.3 could be a marker for early detection of osteomyelitis in infected diabetic foot ulcers patients with.85.6% sensitivity and 77.4% specificity

Conclusion: Procalcitonin/ lactate ratio, which is easy faster and cheaper than MRI could be a good marker for early detection of osteomyelitis in infected diabetic foot ulcer patients with high sensitivity and specificity and a dependable sign for acute DFI.

Keywords: Diabetic foot ulcers, Osteomyelitis, Procalcitonin. Lactate.

INTRODUCTION

The classification method for wound, ischemia, and foot infection-threatening limbs can be used to stage diabetic foot ulcers (DFU). This approach offers risk categorization for major amputation and facilitates communication between clinicians. When infection is suspected, blood tests including a complete blood count (CBC), a thorough metabolic panel, HbA1c and inflammatory markers should be obtained. Get weight-bearing radiographs of the limb that is injured **(1).**

Years of research have not yielded a single adequate criterion for the diagnosis of osteomyelitis in diabetics. Instead, a variety of diagnostic techniques have been employed. Numerous biomarkers have been employed in the identification and assessment of diabetes-related problems **(2).**

In order to diagnose soft tissue and bone infection, widely used test indicators of inflammation around the world include peripheral leukocyte count, erythrocyte sedimentation rate (ESR), CRP, lactic acid, and PCT, may be helpful **(3).**

Due to their lack of specificity, these indicators should not be utilized exclusively to diagnose diabetic foot infections. Instead, the predictive value of additional biomarkers is still necessary. In any event, a decrease in serum marker levels can be used to track a treatment's effectiveness **(4,5).**

Diabetic foot ulcers and soft tissue infections are primarily caused by neuropathy, trauma, inflammatory processes, and in many cases, concurrent peripheral artery occlusive disease **(6).**

PCT has gained popularity as an early diagnostic for sepsis and is recognized as a good marker to distinguish infection from inflammation. Recent studies have focused on the connection between vascular disorders and serum PCT levels **(7).**

Traditionally, lactate has been considered a waste product of anaerobic glycolysis and a sign of ischemia. Lactate buildup in ischemic areas of several vascular disorders has been shown in both patients and animal models **(8).** Therefor in this study, we aimed to assess procalcitonin/ lactic acid ratio as a diagnostic marker in osteomyelitis and soft tissue infection in diabetic foot ulcers.

PATIENTS AND METHODS

Patients: This case control study included 112 type 2

Received: 05/02/2024
Accepted: 04/04/2024

diabetic patients with diabetic foot ulcers attending Diabetic foot outpatient Clinic, Zagazig University. Their ages ranged from 31 to 72 with a mean of 51.2 years, 64 (57.1%) of them were males, 48 (42.9%) of them were females, their body mass indices ranged from 19.3 to 41.4 with a mean of 28.4% and mean duration of diabetes of 13.7 years. Patients in this study were divided into 4 groups: Group (1) included patients with T2DM without foot complications (G1), group (2) included patients with non-infected diabetic foot ulcer (NIDFU) (G2). Soft tissue infection group was further subdivided according to MRI finding into: Group (3) that contained infected diabetic foot without osteomyelitis (G3) and group (4) that included infected diabetic foot with osteomyelitis (G4).

Exclusion Criteria: Patients suffering from sepsis, pneumonia, urinary tract infections, or other systemic or localized infectious illnesses. Individuals who had surgery within the previous six weeks, those with solid or hematological cancers, those with inflammatory illnesses of the system (Inflammatory bowel disease and rheumatoid arthritis) and patients receiving ongoing immunosuppressive treatment. Also, end stage renal disease and chronic liver cell failure.

Ethical Consideration: Zagazig University's Academic and Ethical Committee approved the study. Written informed consent was obtained from each participant. This work has been carried out in accordance with the Helsinki Declaration, the World Medical Association's rule of ethics for research involving human subjects.

METHODS

Operational design: Steps of performance and techniques used:

Every patient underwent a thorough history taking and clinical assessment including general and systemic examination with special stress on blood pressure, pulse, height, weight, BMI [(9)], monofilament-vibration sense by the tuning fork, ankle/brachial index (ABI) for vascular research (dorsalis pedis detection and posterior tibial pulsation) [(10)] and probe-to-bone test (PTB) [(11)].

Laboratory Investigations: All patients in this study were subjected to the following:

(A) Routine investigations in the form of fasting & postprandial plasma glucose level, HbA1c**,** CBC, lipid profile**,** ESR, CRP **and** culture and sensitivity from infected diabetic foot ulcer.

(B) Special investigations in the form of:

1-Procalcitonin level by ELISA.
2-Lactic acid level by using Cobas 6000 fully automated analyzer, serum (Roche Diagnostics).
3-Estimation of procalcitonin lactate ratio.
4-Probe to bone test (PTB).
5-MRI on bone of infected diabetic foot group.

Statistical analysis

The data were imported from Microsoft Excel into the Statistical Package for the Social Sciences (SPSS) version 20.0. Depending on the kind of data, the quantitative group was represented by mean ± SD, while the qualitative group was represented by numbers and percentages. Differences between ANOVA or Kruskal Wallis-based for quantitative independent multiples. The $P \leq 0.05$ for significant results and ≤ 0.001 for highly significant results.

RESULTS

The results of the present study indicated a noteworthy difference between the groups regarding disease duration. There was a significant difference when comparing non-complicated diabetic (G 1) and IDF without osteomyelitis (G 3). Regarding HbA1c, there was a statistically significant difference existed between IDF with osteomyelitis and both of non-IDF and non-complicated diabetic patients.

Regarding white blood cells, there was a statistically significant difference existed between non-complicated DM (G1) and those with IDF (G 4) and without (G 3) osteomyelitis. Also, there was a significant difference between non-IDF (G2) and G3 & G4. Regarding ESR, there was a statistically significant difference among those with IDF and osteomyelitis (G 4) and those without IDF (G 2). There was a significant difference between non-complicated DM (G1) and non-IDF group (G 2) and those with IDF with or without osteomyelitis (G3 & G4). Regarding CRP, there was a statistically significant difference when comparing IDF with (G 4) and without (G 3) osteomyelitis groups (Table 1).

Table (1): Comparison between the studied groups regarding demographic data, routine laboratory tests and acute phase reactants

Parameter	Groups				X^2	Test P
	Non-complicated DM group (G1)	Non infected diabetic foot (NIDF) group (G2)	Infected diabetic footwithout osteomyelitisgroup (G3)	Infected diabeticfoot with osteomyelitis group (G4)		
	N=28(%)	N=28(%)	N=28(%)	N=28(%)		
Sex: Female Male	12 (42.9%) 16 (57.1%)	11 (39.3%) 17 (60.7%)	14 (50%) 14 (50%)	11 (39.3%) 17 (60.7%)	0.875	0.831
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	F	P
Age (year)	47.96 ± 14.18	53.89 ± 12.55	55.21 ± 12.04	49.75 ± 7.05	2.357	0.076
BMI (Kg/m^2)	26.31 ± 5.76	32.93 ± 7.21 [a]	24.27 ± 3.997 [b]	31.14 ± 4.001 [a, c]	5.591	0.001**
Duration (Years)	7.5(5 – 15)	15(5.25 – 18)	18(11.75 – 25)	12(10 – 18)	15.512	<0.001**
HbA1c (%)	7.18 ± 0.97	10.13 ± 2.88 [a]	9.98 ± 2.44	10.65 ± 2.27 [a, b]	13.471	<0.001**
Total cholesterol (mg/dl)	115.72 ± 15.56	142.78 ± 34.2 [a]	230.38 ± 24.85[a, b]	240.64 ± 49.87 [a, b]	96.808	<0.001**
Triglycerides (mg/dl)	127.9 ± 16.67	153.33 ± 7.2 [a]	188.72 ± 32.01[a, b]	178.48 ± 40.5 [a, b]	16.455	<0.001**
LDL cholesterol (mg/dl)	76.67 ± 2.76	96.61 ± 8	148.83 ± 32.4 [a, b]	144.84 ± 4.54 [a, b]	36.581	<0.001**
HDL cholesterol (mg/dl)	34.68 ± 5.4	42.36 ± 3.5 [a]	39.36 ± 5.34 [a]	39.41 ± 6.28 [a]	10.292	<0.001**
WBCs ($x10^3/\mu L$)	8.5(6.05 – 10.5)	10.2(7.4–16.3)	34(18.9 – 45.6)[a, b]	48.4(39.2 – 55.7) [a, b c]	79.537	<0.001**
ESR (mm/h)	6 (4 – 8)	14 (9 – 29.7) [a]	34 (17 – 41) [a, b]	62 (54.26 – 78.33) [a, b, c]	71.327	<0.001**
CRP (mg/dl)	4 (3 – 5)	23 (11 – 43) [a]	120.18(59 –238.3) [a, b]	218.19(69 – 236.5) [a, b, c]	86.59	<0.001**

KW Kruskal Wallis test *p<0.05 is statistically significant. **p≤0.001 is statistically highly significant, a: significant in comparison to G1, b: significant in comparison to G2, c: significant in comparison to G3

Regarding the levels of lactic acid and serum PCT and PCT/ lactic acid ratio, there was a significant difference between non-complicated DM (G1) and those with IDF with or without osteomyelitis (G 3 & G4). Also, there was a significant difference between non-IDF (G 2) and those with IDF with or without osteomyelitis (G3 & G4)**.** Regarding ABI, there was a statistically significant difference among the non-complicated diabetic group (G 1) and both of IDF with and without osteomyelitis (G 3 and G4). There was a significant difference when comparing non-infected diabetic foot group (G2) and IDF with osteomyelitis group (G 4) (Table 2).

Table (2): PCT, lactic acid and PCT/ lactate ratio & ABI among the studied groups

Parameter	Groups				Test	
	Non-complicated DM group (G1)	Non infected diabetic foot (NIDF) group (G2)	Infected diabetic foot without osteomyelitis Group (G3)	Infected diabetic foot with osteomyelitis Group (G4)	KW	p
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)		
PCT (ng/mL)	0.24(0.09–0.46)	0.34(0.07–0.51)	2.9(0.49 – 5.85) [a, b]	10.23(5.1 – 21.5) [a, b,c]	69.146	<0.001**
Lactic acid (mmol/L)	1.65 (1.2–2.1)	1.72 (1.3–2.2)	2.66 (1.9 – 2.9) [a, b]	3.39 (2.6 – 3.9) [a, b,c]	41.28	<0.001**
PCT/ lactate **ratio**	0.15 (0.03–0.25)	0.2 (0.02–0.29)	1.67 (0.08 – 2.1) [a,b]	3.7 (0.22 – 6.46) [a, b, c]	22.64	<0.001**
ABI	1.0 ± 0.2	1.03 ± 0.17	0.85 ± 0.24 [a, b]	0.79 ± 0.26 [a, b]	12.975	<0.001**

F One Way ANOVA test *p<0.05 is statistically significant **p≤0.001 is statistically highly significant, a: significant in comparison to G1, b: significant in comparison to G2, c: significant in comparison to G3

The probe-to-bone (PTB) test demonstrated a sensitivity of 67.9% specificity of 67.9% and positive predictive value of 67.9% for osteomyelitis (Table 3).

Table (3): Study of sensitivity of PTB test in infected soft tissue group for presence of osteomyelitis

MRI		Groups		Test	
		Infected diabetic footwith osteomyelitisGroup by M.R.I (G3)	Infected diabetic foot without osteomyelitis group by M.R.I (G4)	χ^2	p
		N=28(%)	N=28(%)		
Osteomyelitis by probe test:	Positive	19 (67.9%)	9 (32.1%)	7.143	0.008*
	Negative	9 (32.1%)	19 (67.9%)		

χ^2Chi square test *p<0.05 is statistically significant

Serum procalcitonin and all of the following parameters showed a statistically significant positive correlation: WBCs, total cholesterol, LDL cholesterol, triglycerides, CRP and ESR. Serum procalcitonin and ABI had a statistically significant negative correlation (Table 4).

Table (4): Correlation between procalcitonin/lactic acid ratio and the studied parameters

	R	P
Age (Years)	-0.035	0.71
BMI (Kg/m2)	0.044	0.642
Duration (Years)	0.167	0.079
HbA1c (%)	0.356	<0.001**
T. cholesterol (mg/dl)	0.666	<0.001**
Triglycerides (mg/dl)	0.41	<0.001**
LDL (mg/dl)	0.467	<0.001**
HDL (mg/dl)	0.137	0.15
CRP (mg/dl)	0.715	<0.001**
ESR (mm/h)	0.662	<0.001**
ABI	-0.302	<0.001**
WBCs (x10^3/µL)	0.754	<0.001**

**p≤0.001 is statistically highly significant r Spearman rank correlation coefficient

Among factors significantly correlated to serum PCT, only WBCs, triglycerides and total cholesterol significantly independently associated with it (unstandardized β=0.412, -0.045 and -0.031 respectively) (Table 5).

Table (5): Linear stepwise regression analysis of factors significantly associated with procalcitonin/ lactate ratio

	Unstandardized Coefficients		Standardized Coefficients	t	p	95.0% Confidence Interval for B	
	B	SE	Beta			Lower Bound	Upper Bound
(Constant)	**7.373**	**2.251**		**3.275**	**0.001****	**2.910**	**11.836**
WBCs (x10^3/µL)	**0.412**	**0.042**	**0.932**	**9.891**	**<0.001****	**0.330**	**0.495**
Triglycerides (mg/dl)	**-0.045**	**0.015**	**-0.242**	**-2.911**	**0.004***	**-0.076**	**-0.014**
T. cholesterol (mg/dl)	**-0.031**	**0.012**	**-0.248**	**-2.484**	**0.015***	**-0.055**	**-0.006**

**p≤0.001 is statistically highly significant *p<0.05 is statistically significant

With a sensitivity of 94.4%, specificity of 89.9%, accuracy of 88% (p < 0.001) and area under the curve of 0.951, the optimal cutoff of PCT for IDF prediction was ≥ 0.52 ng/ml. With a sensitivity of 93.7%, specificity of 87.5%, accuracy of 87%, and area under the curve of 0.942, the optimal lactic acid cutoff for IDF prediction was ≥ 215 (p<0.001). For the purpose of predicting IDF, the optimal PCT/lactic acid ratio threshold was ≥ 0.004, with an area under the curve of 0.977, sensitivity of 96.2%, specificity of 92.2%, and accuracy of 91% (p<0.001). With an area under the curve of 0.913, sensitivity of 91.7%, specificity of 83.9%, and accuracy of 86% (p<0.001), the optimal cutoff of CRP for IDF prediction was ≥ 36.5 mg/L. With an area under the curve of 0.872, sensitivity of 94.2%, specificity of 80.4%, and accuracy of 85.9% (p<0.001), the optimal cutoff of ESR for IDF prediction is ≥15.35 mm/hr. In patients with diabetic foot, the optimal PCT cutoff for osteomyelitis diagnosis was ≥ 5.9 ng/ml, with a sensitivity of 78.6%, specificity of 69%, area under the curve of 0.859, and accuracy of 81.4% (p<0.001). For patients with diabetic foot, the optimal lactic acid cutoff for osteomyelitis diagnosis was ≥ 315, with an area under curve of 0.814, sensitivity of 74.3%, specificity of 67.8%, and accuracy of 79.3% (p<0.001). For the diagnosis of osteomyelitis in patients with diabetic foot, the optimal PCT/lactic acid ratio threshold was ≥ 0.05, with a sensitivity of 85.4%, specificity of 75.6%, area under the curve of 0.965, and accuracy of 88.6% (p<0.001) (Table 6).

Table (6): Performance of serum PCT, lactic acid, PCT/ lactate ratio, CRP and ESR in diagnosis of patients with infected diabetic foot and in diagnosis of osteomyelitis in patients with diabetic foot

Parameter	Cutoff	AUC	Sensitivity	Specificity	Accuracy	p
patients with infected diabetic foot (group 3)						
PCT (ng/mL)	≥0.52	0.951	94.4%	89.9%	88%	<0.001**
Lactic acid (mmol/L)	≥2.3	0.931	93.2%	87.9%	86%	<0.001**
PCT/ lactate ratio	≥0.31	0.968	95.9%	92.4%	92%	<0.001**
CRP (mg/dl)	≥36.5	0.913	91.7%	83.9%	86%	<0.001**
ESR (mm/h)	≥15.35	0.872	94.2%	80.4%	85.9%	<0.001**
Osteomyelitic Patients with diabetic foot. (group 4)						
PCT(ng/mL)	≥5.9	0.859	78.6%	69%	81.4%	<0.001**
Lactic acid (mmol/L)	**≥3.1**	**0.829**	**75.3%**	**68.2%**	**78.8%**	**<0.001****
PCT/ lactate ratio	≥2.3	0.951	84.6%	77.4%	89.7%	<0.001**
CRP (mg/dl)	≥48.5	0.822	67.3%	61%	71.4%	<0.001**
ESR (mm/h)	≥34.98	0.819	69.3%	66.6%	74.3%	<0.001**

**p≤0.001 is statistically highly significant.

DISCUSSION

Diabetic patients are increasingly experiencing foot infections, which have serious consequences and even lead to lower limb amputation. Sadly, patients who have to amputate a lower limb have relatively bad quality of life, and their five-year mortality rate is comparable to some of the worst cancer types [(12)].

Numerous biomarkers have been employed in the identification and assessment of diabetic complications. When clinical indications are deceptive, WBC, ESR, CRP, PCT, and lactic acid may be useful in the early and non-invasive identification of infection [(2)]. Because these indicators are non-specific, it is not appropriate to utilize them alone to diagnose diabetic foot infections. Instead, novel biomarkers should still be investigated for their potential predictive value [(3)].

Regarding the length of the disease, the current investigation found a statistically significant variation between the groups under analysis. There was a notable distinction when comparing non-complicated diabetic (G 1) and IDFU without osteomyelitis (G 3). In concordance with our study, **Gahlot *et al.*** [(13)] indicated a statistically significant difference in the length of the disease between the groups under study.

According to our research, there was a statistically significant variation in ABI between the groups under investigation. Additionally, in line with our research, **Kristiani *et al.*** [(14)] determined that the degree of the ulcer and ABI had a substantial correlation. The severity of ulcers increases with a lower ABI. Similar to our study, numerous investigations came to the conclusion that individuals with infected DFUs had much greater PCT levels than patients whose ulcers had not become exacerbated by an infection [(2,12,15,16)].

In our study, procalcitonin's optimal cutoff for IDFU prediction was ≥ 0.52 ng/ml, with an area under the curve of 0.951, sensitivity of 94.4%, specificity of 89.9%, and accuracy of 0.951 88% (p<0.001). **Park *et al.*** [(15)] found that in a prospective trial involving 123 patients with infected DFUs, there was a strong correlation found between the degree of infection and both PCT and CRP. But, the ability to differentiate between patients with a systemic infection and those without a concomitant infection was limited to PCT (sensitivity 94.7%, specificity 88.5%, cutoff value 0.59 ng/mL, AUC = 0.869; p < 0.0001). In the study by **Michail *et al.*** [(17)] that enrolled 61 diabetic patients who had infections in their feet. For the diagnosis of diabetic foot osteomyelitis, the sensitivity and specificity were 81% and 71%, respectively, with a threshold value of serum PCT > 30 ng/mL. In contrast, our study found that the optimal PCT cutoff for osteomyelitis diagnosis in patients with diabetic foot was ≥ 5.9 ng/ml with a sensitivity of 78.6%, specificity of 69%, area under the curve of 0.859, and accuracy of 81.4% (p<0.001).

According to the current study, individuals with diabetic foot infections had considerably greater levels of lactic acid than patients without infections, as did patients with diabetic foot with osteomyelitis. In agreement with our study, **Moskowitz *et al.*** [(18)] and **Hafez *et al.*** [(19)] reported that excessive lactate levels frequently imply hypovolemia and microcirculation abnormalities. Leading to that serum lactate levels and PCT may play a crucial role as predictive biomarkers in infection diagnosis. Particularly, the levels of lactate or lactic acid (LA) indicate the severity of severe diseases such as sepsis, cardiovascular emergencies, trauma, and burns [(20, 21)]**.** Measuring lactate levels can help promote early goal-directed therapy (Surviving sepsis campaign) [(22)]**.** When making a clinical diagnosis or prediction, professionals may find it useful to combine many indicators. The relative PCT concentration that was modified for stress and long-term issues brought on by the illness itself may be the source of the Procalcitonin/Lactic Acid Ratio's (PLR) potential importance. Infected diabetic foot can be identified using PCT (threshold > 0.52), lactic acid (threshold > 2.3), and PLR (threshold > 0.31), and combining these

two markers may improve specificity. increased PLR in individuals with DFU infection should warrant the presence of osteomyelitis in these patients and advanced radiological investigations such as MRI of infected foot are required.

In agreement with our study, **Huang *et al.*** [(23)] demonstrated that in diabetes ketoacidosis (DKA) patients, PLR had a good diagnostic effectiveness for infection, demonstrating the new factor's suitability as a sepsis marker. Also, those who have DKA as a result of diabetes may be able to diagnose infection in its early stages by using a PLR threshold level of > 0.438**.** According to a Chinese study, the PLR of individuals with infection and diabetes was 0.25 ± 0.11%, significantly greater than the group under control ($p < 0.05$). Furthermore, PLR demonstrated a high sensitivity of 84.46% and specificity of 87.23% for the identification of infection-related diabetes [(24)].

CONCLUSION

Procalcitonin/ lactate ratio, which is fast, easy and cheaper than MRI could be good marker for early detection of osteomyelitis in infected diabetic foot ulcer patients with high sensitivity and specificity and a dependable sign for acute DFI.

- **Conflict of interest:** None.
- **Funding sources:** No specific grant from governmental, private, or nonprofit organizations was obtained for this study.
- **Author contribution:** Each author made an equal contribution in the research.

REFERENCES

1. **Gentile T, Berman S, Reinke R *et al.* (1998):** A regional pedal ischemia scoring system for decision analysis in patients with heel ulceration. Am J Surg., 176 (2): 109-14.
2. **Massara M, DE Caridi G, Serra R *et al.* (2017):** The role of procalcitonin as a marker of diabetic foot ulcer infection. Int. Wound J., 14: 31–34.
3. **Pichu S, Patel M, Apparsundaram S *et al.* (2017):** Role of biomarkers in predicting diabetes complications with special reference to diabetic foot ulcers. Biomark. Med., 11:377–88.
4. **Van Asten A, Nichol A, La Fontaine J *et al.* (2017):** The value of inflammatory markers to diagnose and monitor diabetic foot osteomyelitis. Int. Wound J., 14: 40–45.
5. **Jafari J, Firouzabadi S, Izadi M, *et al.* (2014):** Can procalcitonin be an accurate diagnostic marker for the classification of diabetic foot ulcers? J Clin Endocrinol Metab,, 12 (1): 96-108.
6. **Bandyk F (2018):** The diabetic foot: Pathophysiology, evaluation, and treatment. Semin. Vasc. Surg., 31 (2-4): 43-48.
7. **Kurtul A, Elcik D (2017)**: Procalcitonin is an independent predictor for coronary atherosclerotic burden in patients with stable coronary artery disease. *Int. J. Cardiol.*, *236*, 61-64.
8. **Taher M, Leen G, Wevers A *et al.* (2016):** Lactate and its many faces. Eur. J. Paediatr. Neurol., 20(1): 3-10.
9. **Yan X, Song F, Zhang L *et al.* (2022):** Analysis of risk factors for multidrug-resistant organisms in diabetic foot infection. BMC Endocr. Disord., 22(1): 46.
10. **Flores-Escobar S, López-Moral M, García-Madrid M *et al.* (2024):** Diagnostic Performance of Atherogenic Index of Plasma for Predicting Diabetic Foot Osteomyelitis with Peripheral Artery Disease. J. Clin. Med., 13(7): 1934.
11. **Calvo-Wright M, Álvaro-Afonso J, López-Moral M *et al.* (2023):** Is the Combination of Plain X-ray and Probe-to-Bone Test Useful for Diagnosing Diabetic Foot Osteomyelitis? A Systematic Review and Meta-Analysis. J. Clin. Med., 12(16): 5369.
12. **Kim Y, Lee S, Ahn S *et al.* (2011):** The usefulness of procalcitonin and C-reactive protein as early diagnostic markers of bacteremia in cancer patients with febrile neutropenia. *Cancer Res Treat.*, 43(3):176-80.
13. **Gahlot G, Ram P, Parmar D *et al.* (2021):** Significant Role of Procalcitonin and Proinflammatory Markers in Diabetic Foot Ulcer Infections. *Int. J. Inn. Res., (IJIRMS)*, *6*:10.
14. **Kristiani L, Sumangkut M, Limpeleh P (2015):** Hubungan ankle brachial index dengan keparahan ulkus pada penderita kaki diabetik. J. Biomedik., 7: 171–177.
15. **Park H, Suh H, Kim J *et al.* (2017):** Role of procalcitonin in infected diabetic foot ulcer. Diabetes Res. Clin. Pract., 128:51–7.
16. **Al-Shammaree W, Abu-Alkaseem B, Salman I (2017):** Procalcitonin levels and other biochemical parameters in patients with or without diabetic foot complications.J. Res. Med. Sci., 22:95.
17. **Michail M, Jude E, Liaskos C *et al.* (2013):** The performance of serum inflammatory markers for the diagnosis and follow-up of patients with osteomyelitis. Int. J. Low. Extrem. Wounds, 12:94–9.
18. **Moskowitz A, Graver A, Giberson T *et al.* (2014):** The relationship between lactate and thiamine levels in patients with diabetic ketoacidosis. J. Crit. Care, 29(1): 5-8.
19. **Abdel Hafez A, Qedra S, Ismael K *et al.* (2023):** Predictive Value of Sepsis Markers in Diabetic Ketoacidosis Patients Admitted to Intensive Care Unit. EJHM., 90(2): 2074-2079.
20. **Unal E, Pirinccioglu G, Yanmaz Y *et al.* (2020):** A Different Perspective of Elevated Lactate in Pediatric Patients with Diabetic Ketoacidosis. Acta Endocrinol., 16, 114–117.
21. **Ibrahim A, Bayramoglu B, Hokenek N *et al.* (2021):** Lactate clearance during the first 2 hours after hospital admission: A useful biomarker for predicting 30-day mortality in patients with diabetic ketoacidosis. Int. J. Clin. Pract., 75(7):e14204. doi: 10.1111/ijcp.14204.
22. **Rhodes A, Evans L, Alhazzani W *et al.* (2017):** Surviving sepsis campaign: international guidelines for the management of sepsis and septic shock: 2016. Intensive Care Med.,43(3):304-77.
23. **Huang B, Yang S, Ye S (2022):** Systemic Infection Predictive Value of Procalcitonin to Lactic Acid Ratio in Diabetes Ketoacidosis Patients. Diabetes Metab. Syndr. Obes., 15: 2127–2133.
24. **Wang Y, Wang F, Li G *et al.* (2019):** Effect of ratio of serum procalcitonin to lactic acid on diagnosis of infection in patients with diabetic ketoacidosis. Chin. J. Nosocromiology, 29: 1347–1350.