

ORIGINAL ARTICLE

Analysis of routine blood markers for predicting amputation/re-amputation risk in diabetic foot

Anıl Gülcü¹ | Mustafa Etli² | Oğuz Karahan² | Ahmet Aslan¹

¹Department of Orthopaedics and Traumatology, Alanya Alaaddin Keykubat University, Alanya, Turkey

²Department of Cardiovascular Surgery, Alanya Alaaddin Keykubat University, Alanya, Turkey

Correspondence

Anıl Gülcü, MD, Assistant Prof. Dr, Alanya Alaaddin Keykubat University, Faculty of Medicine, Department of Orthopaedics and Traumatology, 07425-Alanya, Turkey.
Email: anilgulcu@gmail.com

Abstract

Diabetic foot is challenging progressive disease which requires multisystemic control. Neuropathy, arteriopathy, and cellular responses should be treated collaboratively. Despite all medical advances, diabetic foot can highly result in amputation and also re-amputation can be required because of failed wound healing. In this study, we aimed to investigate the relation between blood parameters and amputation events. Diabetic 323 patients included in the study who referred to orthopaedic clinic for amputation. Amputation levels (amputation levels phalanx, metatarsal, Lisfranc, syme, below knee, knee-disarticulation, above-knee amputation) and re-amputations recorded and compared with routine blood parameters. Re-amputation was observed in 69 patients. The significant difference detected between lower albumin, higher HbA1c, higher CRP levels ($P < 0.05$) in regards to gross amputation levels, and increased wound depth. Furthermore, lower albumin levels and higher levels of WBC, HbA1c, CRP, and Creatinine were detected in re-amputation levels. Especially, HbA1c, CRP, and Creatinine levels were found as upper bound of reference line for re-amputation. The statistically optimal HbA1c cutoff point for diabetes was $\geq 7.05\%$, with a sensitivity of 86% and a specificity of 59%. In accordance with our results, simple blood parameters can be useful for observing the progress of amputation in diabetic foot. Particularly, lower albumin, and higher HbA1c, CRP, and Creatinine levels detected as related with poor prognosis. Besides, screening of HbA1c level seems to be highly sensitive for detecting of re-amputation possibility.

KEYWORDS

amputation levels, blood parameters, diabetic foot, HbA1c, re-amputation

1 | INTRODUCTION

Diabetes is a worldwide problem that affects multiple organ systems and is a component of the challenging syndromes such as metabolic syndrome.¹ Also neuronal system, renal system, arterial system (which implicates organ perfusion), retinal tissue, and wound healing are

affected by hyperglycemia due to insulin.^{1,2} Especially wound healing processes are affected in different steps and it leads to nonhealing ulcers which can be ended in extremity loss. Some causes of nonhealing ulcerative wounds can be listed as colonisation of microorganisms, disintegration of injured epithelial barrier, disrupted immune defence, and functional abnormalities at

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2020 The Authors. *International Wound Journal* published by Medicalhelplines.com Inc (3M) and John Wiley & Sons Ltd.

connective and subcutaneous tissue. When combined of these underlying wound pathologies with neuropathy and impaired vascular flow, diabetic wounds are usually occurs at feet which is named as diabetic foot.¹⁻³

Cellular healing mechanisms has affected in diabetic patients. Toxic potential of higher blood glucose levels against fibroblasts and mitochondrial activity has already shown.³⁻⁵ The increased blood glucose leads to producing of reactive oxygen species and break down oxidative balance. Antioxidant capacity is reduced and cellular senescence and apoptosis is triggered.^{3,6-8} Thus, wounds are not healing regularly and that can be result with comorbidities such as diabetic foot. Nonhealed ulcers can be resulted with extremity loose, because of infection and insufficient oxygenation.³⁻⁷ Moreover, impaired wound healing leads to re-amputations in treated segments which was amputated formerly for treatment of gangrene and infection. In previous studies, investigators focused on the possible blood predictors for determining to the re-amputation requirement. Serum albumin, haemoglobin (Hb), white blood cell count (WBC), neutrophils, neutrophil/lymphocyte ratio, C-reactive protein (CRP) levels, and also glycated haemoglobin (HbA1c) levels as predictor of glucose metabolism were studied in previous studies.⁹⁻¹¹ In according to obtained results of these previous studies, impaired blood glucose control and unregulated HbA1c was found as one of strong predictor for predicting to re-amputation in diabetic patients.⁹⁻¹¹

Thus, in this study we aimed to investigate the relationship between routinely tested blood markers and re-amputation rates in diabetic foot patients. Additionally, we targeted to sensitivity and specificity of these markers for predicting to determining re-amputation probability in diabetic foot patients who had previous amputation history.

2 | MATERIAL AND METHOD

Ethical approval was obtained from human ethical committee of University. The study protocols were designed in according to Helsinki Declaration and in adherence to local guidelines for good clinical practice. After determination of all steps, the diabetic foot patients who admitted to orthopaedic clinic for extremity amputation were recorded retrospectively between 2003 and 2018. Type 2 diabetes mellitus cases, diabetic foot patients with requirement of amputation, and patients available for past medical records at least 2 years were detected as inclusion criteria. Traumatic or nondiabetic amputations, patients with nonrecorded first amputation, and patients with other systemic diseases (malignancies, immune syndromes etc.) were excluded from the study. After included to the study the demographical findings, depth of wound, duration of diabetes were recorded.

Key Messages

- Diabetic foot is an important disorder that can result with high mortality and morbidity rates if it is not timely diagnosed and treated.
- The simple blood markers can be beneficial for follow up to the progression disease. Higher HbA1C, (C-reactive protein) CRP and creatinine levels seems to be related with bad prognosis.
- Risk groups can be follow up with these parameters. As a result of our findings HbA1C is the most sensitive predictor for reamputation in diabetic foot patients.

2.1 | Staging

The Wagner-Meggitt classification system was used for diabetic foot classification.¹² Health status and comorbidity of patients were classified in according to ASA criteria.¹³

The decision of amputation and/or re-amputation was given from the diabetic foot committee in according to following criteria:

- Clinical findings; gangrenous colour changes of skin, foul smell relates to anaerobic colonisation; necrosis; progressive unresponsive septic or toxic clinic in spite of medical treatment.
- Diagnostic markers; Irreversible ischemic changes that was supported with ankle-brachial index evaluation (lower than 0.8) and illustrated with vascular Doppler ultrasound.
- After determining the appropriately perfused and noninfected area amputation levels were selected as: Digital (phalanx), Ray amputation, Trans-metatarsal, Lisfranc, Syme's, Trans-tibial (below knee), Knee disarticulation, and Trans-femoral (above knee).

After operation every patients was taken into orthopaedic clinics and collaboratively followed up for blood glucose and blood parameters regulation, daily wound dressing, rehabilitation, and prosthesis application if it is necessary. Completely healed skin lesions and nonrecurrence at least following 6 months were accepted as total cure.

2.2 | Blood parameters

Retrospectively routine blood parameters before application of amputation were controlled. Haemoglobin

(Hb) [g/dL], white blood cell count (WBC) [K/ μ L], Albumin [g/dL], Glycated haemoglobin (HbA1c) (%), C-reactive protein (CRP) [mg/dL], and creatinine [mg/dL] levels were recorded.

2.3 | Statistical analyse

All collected data were analysed by using SPSS software program (ver. 15.0, Chicago, Illinois). Continuous values expressed as mean \pm SD and categorical values were expressed with percentages. The differences between groups were analysed with using Mann–Whitney *U* test. Optimal cut-off value of significant parameters for predicting amputations/re-amputations with expressing maximum sensitivity and specificity were detected by using receiver operator characteristic (ROC) curve analysis. Accuracy of test was detected with using area under curve (AUC) values. The statistical significance was considered in according *p* values smaller than 0.05.

3 | RESULTS

Totally 323 patients were included to the study. The mean age of patients was found as 64.01 ± 12.17 . Gender distribution was detected as 94 (29%) female and 229 (71%) male. The involved side was found as

147 (45.5%) left, 168 (52%) right, 8 (2.5%) bilaterally. The amputation levels were listed at Table 1 and depth of wounds presented at Table 2.

The statistical difference was significant between amputation levels in regards of albumin, HbA1c, CRP, and creatinine levels ($P < 0.001$). Below knee and higher segment of amputation groups has lower albumin levels when compared with foot level amputation groups. Moreover, HbA1c (%) levels were detected as <7.0 in foot level amputation groups and >7.5 in below knee and higher segment of amputation groups ($P < 0.001$). Consecutively, CRP and creatinine levels were detected as ≤ 4.04 and ≤ 1.74 mg/dL in foot level amputation groups and ≥ 5.13 and ≥ 1.98 mg/dL in below knee and higher segment of amputation groups ($P < 0.001$). There is no significant differences between amputation levels in regards of haemoglobin and WBC levels. The distribution of amputation levels and laboratory markers listed at Table 3.

There was a significant difference between wound depth classes in regards of albumin, HbA1c, and CRP levels ($P < 0.001$). Increased depth of wound groups^{4,5} has lower albumin levels when compared with lower depth wound (1, 2, and 3) groups. Moreover, HbA1c (%) levels were detected as <7.0 in lower depth wound groups and >7.5 in higher depth wound groups ($P < 0.001$). Consecutively, CRP and creatinine levels were detected as ≤ 4.40 and ≤ 1.52 mg/dL in lower depth wound groups and ≥ 4.91 and ≥ 2.22 mg/dL in higher depth wound groups ($P < 0.001$). There is no significant differences between amputation levels in regards of haemoglobin and WBC levels. The distribution of wound depths and laboratory markers listed at Table 4.

There was a significant difference between American Society of Anaesthesiologists Classification (ASA) groups in regards of albumin, creatinine, HbA1c, and CRP levels ($P < 0.001$). Patients in higher ASA classes^{4,5} has lower albumin levels when compared with lower ASA (1, 2, and 3) classes. Moreover, HbA1c (%) levels were detected as <7.24 in lower ASA classes and >7.86 in higher ASA classes ($P < 0.001$). Consecutively, CRP and creatinine levels were detected as ≤ 4.59 and ≤ 1.99 mg/dL in lower ASA classes and ≥ 4.92 and ≥ 2.49 mg/dL in higher ASA classes ($P < 0.001$). There is no significant differences between amputation levels in regards of haemoglobin and WBC levels. The distribution of ASA classes and laboratory markers listed at Table 5.

The 69 of the patients (21%) had re-amputation. All laboratory parameters were found as statistically significant except Hb levels when compared re-amputation required patients with stable patients who does not required re-amputation. The lower albumin levels and Higher WBC, HbA1c, CRP, and creatinine levels detected in re-amputation group. Duration of diabetes was detected as 15.5 ± 11.6 years in re-amputation group and 8.64 ± 8.1 years in stable group

TABLE 1 Amputation levels of patients

Level	<i>n</i>	%
Phalanx	49	15.2
Trans-metatarsal	38	11.8
Lisfranc	45	13.9
Syme's	56	17.3
Below knee	81	25.1
Knee disarticulation	16	5.0
Above knee	38	11.8
Total	323	100.0

TABLE 2 Depth of wound

Depth of Wound	<i>n</i>	%
1	10	3.1
2	51	15.8
3	115	35.6
4	108	33.4
5	39	12.1
Total	323	100.0

TABLE 3 Laboratory findings for each amputation segments groups

Blood Parameter	Amputation Segment	n	Mean \pm Std. Deviation	95% Confidence Interval for Mean	
				Lower Bound	Upper Bound
Albumin (g/dL)	Phalanx	49	4.314 \pm 0.5842	4.146	4.482
	Trans-metatarsal	38	3.895 \pm 0.7472	3.649	4.140
	Lisfranc	45	3.953 \pm 0.6262	3.765	4.141
	Syme's	57	3.936 \pm 0.7547	3.734	4.138
	Below knee	81	3.389 \pm 0.7475	3.224	3.554
	Knee disarticulation	16	3.400 \pm 0.6763	3.040	3.760
	Above knee	37	3.296 \pm 0.6450	3.081	3.511
WBC (K/ μ L)	Phalanx	49	9576.22 \pm 4880.237	8174.45	10 977.99
	Trans-metatarsal	38	11 430.79 \pm 4406.613	9982.37	12 879.21
	Lisfranc	45	9832.22 \pm 4078.011	8607.05	11 057.39
	Syme's	57	10 712.50 \pm 3566.059	9757.50	11 667.50
	Below knee	81	10 620.42 \pm 3357.602	9877.99	11 362.85
	Knee disarticulation	16	10 740.00 \pm 3660.810	8789.29	12 690.71
	Above knee	37	10 209.74 \pm 3917.484	8922.09	11 497.38
Hb (g/dL)	Phalanx	49	13.047 \pm 1.3516	12.659	13.435
	Trans-metatarsal	38	17.195 \pm 21.5291	10.118	24.271
	Lisfranc	45	14.200 \pm 14.2459	9.920	18.480
	Syme's	57	12.368 \pm 1.7608	11.896	12.839
	Below knee	81	12.662 \pm 11.8918	10.032	15.291
	Knee disarticulation	16	11.194 \pm 2.0728	10.089	12.298
	Above knee	37	11.415 \pm 1.6981	10.857	11.973
HbA1c (%)	Phalanx	49	6.676 \pm 0.3370	6.579	6.772
	Trans-metatarsal	38	7.105 \pm 0.5959	6.909	7.301
	Lisfranc	45	7.044 \pm 0.5101	6.891	7.198
	Syme's	57	7.005 \pm 0.5658	6.854	7.157
	Below knee	81	7.574 \pm 0.6294	7.434	7.714
	Knee disarticulation	16	7.833 \pm 0.4716	7.572	8.094
	Above knee	37	7.665 \pm 0.6826	7.427	7.903
CRP (mg/dL)	Phalanx	49	4.2000 \pm 3.87604	3.0216	5.3784
	Trans-metatarsal	38	4.0441 \pm 2.76287	3.0801	5.0081
	Lisfranc	45	3.8619 \pm 3.40587	2.8006	4.9232
	Syme's	57	3.5942 \pm 2.83579	2.8047	4.3837
	Below knee	81	5.1338 \pm 3.87073	4.2552	6.0123
	Knee disarticulation	16	6.6733 \pm 4.07492	4.4167	8.9299
	Above knee	37	6.6778 \pm 4.70496	5.0858	8.2697
Creatinine (mg/dL)	Phalanx	49	1.1340 \pm 0.38533	1.0140	1.2541
	Trans-metatarsal	38	1.5252 \pm 0.85977	1.2098	1.8405
	Lisfranc	45	1.5992 \pm 1.52205	1.1058	2.0926
	Syme's	57	1.7430 \pm 1.52796	1.2944	2.1916
	Below knee	81	1.9836 \pm 1.29853	1.6828	2.2845
	Knee disarticulation	16	2.2554 \pm 1.52401	1.3344	3.1763
	Above knee	37	2.5612 \pm 1.76023	1.9371	3.1854

TABLE 4 Laboratory findings for each wound depth groups

Blood Parameters	Wound Depth	n	Mean \pm Std. Deviation	95% Confidence Interval for Mean	
				Lower Bound	Upper Bound
Albumin (g/dL)	1	10	4.260 \pm 0.6204	3.816	4.704
	2	51	4.250 \pm 0.5881	4.083	4.417
	3	115	3.945 \pm 0.6911	3.818	4.073
	4	108	3.433 \pm 0.7035	3.299	3.568
	5	39	3.307 \pm 0.8382	3.035	3.578
WBC (K/ μ L)	1	10	10 054.03 \pm 5876.307	5850.37	14 257.68
	2	51	10 031.18 \pm 4102.948	8877.20	11 185.15
	3	115	10 271.91 \pm 4076.491	9518.87	11 024.96
	4	108	10 902.86 \pm 3858.830	10 166.77	11 638.95
	5	39	10 131.03 \pm 3178.728	9100.60	11 161.45
Hb (g/dL)	1	10	13.490 \pm 1.2270	12.612	14.368
	2	51	12.878 \pm 1.3296	12.504	13.252
	3	115	12.190 \pm 1.6787	11.880	12.500
	4	108	14.046 \pm 15.8954	11.014	17.078
	5	39	14.160 \pm 17.0349	8.638	19.682
HbA1c (%)	1	10	6.670 \pm 0.1829	6.539	6.801
	2	51	6.743 \pm 0.4010	6.628	6.858
	3	115	6.982 \pm 0.5262	6.885	7.080
	4	108	7.542 \pm 0.5974	7.426	7.657
	5	39	7.839 \pm 0.6549	7.624	8.055
CRP (mg/dL)	1	10	4.3600 \pm 5.19020	.6472	8.0728
	2	51	3.8277 \pm 3.33360	2.8489	4.8064
	3	115	3.9398 \pm 3.22132	3.3102	4.5694
	4	108	4.9772 \pm 3.72290	4.2423	5.7122
	5	39	7.0564 \pm 4.42230	5.6229	8.4900
Creatinine (mg/dL)	1	10	1.0340 \pm 0.38687	0.7572	1.3108
	2	51	1.2591 \pm 0.48156	1.1127	1.4055
	3	115	1.5218 \pm 1.39475	1.2361	1.8075
	4	108	2.2232 \pm 1.49376	1.9206	2.5259
	5	39	2.2174 \pm 1.40678	1.7342	2.7007

($P < 0.001$). Comparison of laboratory parameters in regards of re-amputation was presented at Table 6.

HbA1c, creatinine, and CRP levels were found as upper to reference line in ROC curve analyse (Figure 1). The cut-off values were determined for predictor potential of these parameters for re-amputation. The optimal cut-off value of serum HbA1C levels was found as >7.05 for predicting re-amputation with 86.7% sensitivity and 59.0% specificity (AUC: 0.785, 95% CI: 0.728–0.842). The optimal cut-off value of serum CRP levels was found as >4.05 mg/dL for predicting re-amputation with 61.2%

sensitivity and 63.5% specificity (AUC: 0.627, 95% CI: 0.550–0.704). The optimal cut-off value of serum creatinine levels was found as >1.60 mg/dL for predicting re-amputation with 56.6% sensitivity and 69.0% specificity (AUC: 0.690, 95% CI: 0.609–0.770).

4 | DISCUSSION

Our results indicate that there can be a strong relationship between higher HbA1C, (C-reactive protein) CRP and

TABLE 5 The distribution of laboratory markers in regards of American Society of Anesthesiologists Classification (ASA)

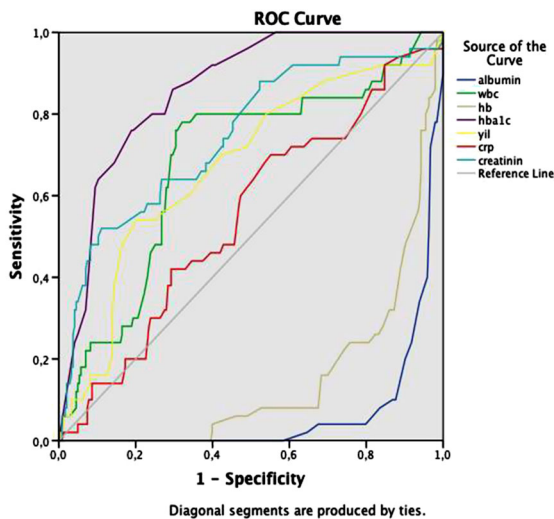
Blood Parameters	ASA Class	n	Mean ± Std. Deviation	95% Confidence Interval for Mean	
				Lower Bound	Upper Bound
Albumin (g/dL)	1	6	3.177 ± 0.8841	2.249	4.104
	2	135	4.124 ± 0.6573	4.012	4.236
	3	113	3.633 ± 0.7213	3.498	3.768
	4	64	3.352 ± 0.7217	3.171	3.534
	5	5	2.625 ± 0.1500	2.386	2.864
WBC (K/ μ L)	1	6	11 005.00 ± 2944.240	7915.21	14 094.79
	2	135	10 266.98 ± 4291.934	9533.61	11 000.34
	3	113	10 404.28 ± 3755.047	9704.37	11 104.19
	4	64	10 675.87 ± 3795.428	9720.01	11 631.74
	5	5	11 900.00 ± 4874.423	4143.71	19 656.29
Hb (g/dL)	1	6	12.687 ± 1.1897	11.438	13.935
	2	135	12.476 ± 1.7372	12.179	12.773
	3	113	11.894 ± 1.7046	11.576	12.212
	4	64	17.506 ± 24.2447	11.400	23.612
	5	5	9.150 ± 1.5000	6.763	11.537
	Total	323	13.223 ± 11.0119	12.012	14.434
HbA1c (%)	1	6	7.050 ± 0.2168	6.822	7.278
	2	135	6.890 ± 0.5331	6.799	6.981
	3	113	7.246 ± 0.5758	7.138	7.353
	4	64	7.864 ± 0.5438	7.721	8.007
	5	5	8.350 ± 0.1000	8.191	8.509
CRP (mg/dL)	1	6	3.5000 ± 1.00797	2.4422	4.5578
	2	135	3.8254 ± 3.16579	3.2672	4.3836
	3	113	4.5909 ± 3.32026	3.9287	5.2531
	4	64	6.5871 ± 5.01965	5.3123	7.8618
	5	5	4.9250 ± 1.25000	2.9360	6.9140
Creatinine (mg/dL)	1	6	1.3400 ± 0.56551	0.7465	1.9335
	2	135	1.2484 ± 0.60655	1.1368	1.3599
	3	113	1.9936 ± 1.60359	1.6669	2.3202
	4	64	2.4945 ± 1.63402	2.0569	2.9321
	5	5	3.0000 ± 2.09523	-2.2048	8.2048

creatinine levels, and higher-level amputations in diabetic foot patients. Moreover, it seems to be that wound depth strongly associated that lower albumin, and higher HbA1C, CRP levels. Another quite remarkable finding of our study is related about prediction re-amputation rates with increased value of serum HbA1C (with a cut-off value of), CRP (with a cut-off value of 4.05), and creatinine (with a cut-off value of 1.6) levels. Especially, in according to our results HbA1C is the most sensitive predictor for re-amputation in diabetic foot (optimal cut-off value: 7.05 with 86% sensitivity and 59% specificity).

Previous studies also focused to investigate blood parameters for determining to prognosis of diabetes and also diabetic foot. Icer et al found that albumin, haemoglobin, WBC, neutrophils, neutrophil/lymphocyte ratio, HbA1c levels were related extremity amputation.⁹ Also, they claimed that disease duration is related amputation because of impaired glucose metabolism.⁹ In previous studies, lower albumin levels were associated with poor prognosis for many kind of circulatory problems.^{14,15} In in vitro models reduced albumin levels were related with increased plasma protein glycation and also

Laboratory Parameter	Re-amputation	Mean ± Std. Deviation	P
Albumin (g/dL)	-	3.896 ± 0.7339	0.001
	+	3.230 ± 0.6939	
WBC (K/μL)	-	10 024.13 ± 3942.656	0.001
	+	11 882.46 ± 3725.957	
Hb (g/dL)	-	12.599 ± 6.8135	0.250
	+	15.402 ± 19.7597	
HbA1c (%)	-	7.082 ± 0.6098	0.001
	+	7.760 ± 0.5766	
CRP (mg/dL)	-	4.2828 ± 3.53533	0.001
	+	6.1090 ± 4.24402	
Creatinine (mg/dL)	-	1.5702 ± 1.12674	0.001
	+	2.5660 ± 1.80507	

TABLE 6 Comparison of the re-amputation and stabile groups



Test Result Variable(s)	Area	Asymptotic 95% Confidence Interval	
		Lower Bound	Upper Bound
Hba1c	0,785	0,728	0,842
Crp	0,627	0,550	0,704
Creatinin	0,690	0,609	0,770

FIGURE 1 The ROC curve analyses of blood parameters for prediction re-amputation in diabetic foot

negatively correlated with increased HbA1c levels.¹⁶ In another study lower albumin levels were associated with poorly controlled diabetes and also elevated HbA1c levels.¹⁰ Also, low serum albumin levels were suggested as a risk factor for nonhealing diabetic foot ulcers and poor prognosis.¹⁷ The other study about length of hospital stay in diabetic foot found that WBC count, CRP levels, and albumin levels were strongly correlated with

long term hospital stay.¹⁸ Furthermore, poor prognosis predictors decremental albumin levels and incremental HbA1c are strongly related with elevated plasma protein glycation that irreversibly impairs the wound healing physiology from cells-to-organs. Also wound healing mechanisms; as migration, proliferation, and trans-differentiation steps are affected due to the toxic effects of impaired blood glucose control.⁵ Also, CRP as predictor for active inflammation was shown as a risk factor for amputation in diabetic foot ulcers.¹¹ Similarly, Volaco et al, suggested that higher CRP levels are strong predictor for major amputation for patients with ischemic diabetic foot lesions.¹⁹ In another study increased levels of WBC and CRP was associated with poor prognosis and therapeutic failure of diabetic foot ulcers.²⁰ Additionally, in another study it was claimed that lower serum albumin levels show also poor prognosis and associated with increased amputation risk.²¹ Likewise, HbA1c well-known marker of detecting glycaemic control for last 2 to 3 months, have gained importance and have been comprehensively investigated in relation with diabetic foot ulcers, gangrene, and limb amputation.²² There are several conflicting reports about amputation risk and HbA1c levels in literature. Nerone et al, detected that major amputations was not affected to elevated HbA1c levels.²³ Similarly, O'Connor et al found that there was not significant relation between HbA1c levels and risk of peripheral artery disease (PAD) and re-intervention requirement in patients with critical limb ischemia.²⁴ Oppositely, it was shown that HbA1c levels was an independent risk factor for determining to the amputation level as below knee or above knee in Nather et al's research.²⁵ Similarly, we found that elevated HbA1C closely related with higher level of extremity amputation and independent predictor

for re-amputation in patients with diabetic foot. As supporting data of our findings, there was an evidence based results that determines 1% increase in HbA1c levels is associated 26% increases in the prevalence of PAD which can be directly related with higher risk of major limb loss.²⁶ Almost the similar with literature we found significantly lower albumin levels, and markedly higher WBC, HbA1c, CRP, and creatinine levels, and longer disease durations in re-amputation patients with diabetic foot ulcers. Even, we found that HbA1C, CRP, and creatinine are sensible laboratory markers for amputation.

In conclusion the main point for amputation and/or re-amputation for diabetic foot ulcers seems to be related with impaired glucose metabolism. The reflective blood parameters about this point such as albumin, WBC, CRP, and HbA1c can be useful for determining to the amputation risk. Especially, we suggest that higher HbA1c levels is highly sensitive for predicting to the amputation risk, in according to our results.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ORCID

Anıl Gülcü  <https://orcid.org/0000-0002-9012-8053>

Mustafa Etili  <https://orcid.org/0000-0001-9320-3971>

Oğuz Karahan  <https://orcid.org/0000-0003-0044-9476>

Ahmet Aslan  <https://orcid.org/0000-0001-5797-1287>

REFERENCES

- Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. *Lancet*. 2005;366(9498):1719-1724.
- O'Loughlin A, McIntosh C, Dinneen SF, O'Brien T. Review paper: basic concepts to novel therapies: a review of the diabetic foot. *Int J Low Extrem Wounds*. 2010;9(2):90-102. <https://doi.org/10.1177/1534734610371600>.
- Falanga V. Wound healing and its impairment in the diabetic foot. *Lancet*. 2005;366(9498):1736-1743.
- Brem H, Tomic-Canic M. Cellular and molecular basis of wound healing in diabetes. *J Clin Invest*. 2007;117(5):1219-1222.
- Berlanga-Acosta J, Schultz GS, López-Mola E, Guillen-Nieto G, García-Siverio M, Herrera-Martínez L. Glucose toxic effects on granulation tissue productive cells: the diabetics' impaired healing. *Biomed Res Int*. 2013;2013:256043. <https://doi.org/10.1155/2013/256043>.
- Tesfaye S, Selvarajah D. Advances in the epidemiology, pathogenesis and management of diabetic peripheral neuropathy. *Diabetes Metab Res Rev*. 2012;28(Suppl 1):8-14.
- Baltzis D, Eleftheriadou I, Veves A. Pathogenesis and treatment of impaired wound healing in diabetes mellitus: new insights. *Adv Ther*. 2014;31(8):817-836.
- Ma L, Li P, Shi Z, Hou T, Chen X, Du J. A prospective, randomized, controlled study of hyperbaric oxygen therapy: effects on healing and oxidative stress of ulcer tissue in patients with a diabetic foot ulcer. *Ostomy Wound Manage*. 2013;59(3):18-24.
- Icer M, Durgun HM. Factors affecting amputations in patients with diabetic foot ulcer referring to the emergency units. *Dicle Med J*. 2017;44(1):91-97.
- Rodríguez-Segade S, Rodríguez J, Mayan D, Camiña F. Plasma albumin concentration is a predictor of HbA1c among type 2 diabetic patients, independently of fasting plasma glucose and fructosamine. *Diabetes Care*. 2005;28(2):437-439.
- Maragathamani AA. Correlation of CRP level with glycemic control in diabetic foot patients and its sequelae. *Int Surg J*. 2017;4(12):4006-4009.
- Jain AKC. A new classification of diabetic foot complications: a simple and effective teaching tool. *J Diab Foot Compl*. 2012;4:1-5.
- Doyle DJ, Garmon EH, Bansal P, Garmon EH. American Society of Anesthesiologists Classification (ASA Class). *StatPearls [Internet]*. Treasure Island (FL): StatPearls Publishing; 2020. PMID: 28722969.
- Karahan O, Yavuz C, Kankilic N, et al. Simple blood tests as predictive markers of disease severity and clinical condition in patients with venous insufficiency. *Blood Coagul Fibrinolysis*. 2016;27(6):684-690.
- Karahan O, Acet H, Ertaş F, et al. The relationship between fibrinogen to albumin ratio and severity of coronary artery disease in patients with STEMI. *Am J Emerg Med*. 2016;34(6):1037-1042.
- Bhonsle HS, Korwar AM, Kote SS, et al. Low plasma albumin levels are associated with increased plasma protein glycation and HbA1c in diabetes. *J Proteome Res*. 2012;11(2):1391-1396.
- Edakkepuram U, Sheeja PC, Gopi EV. A prospective cohort study of hypoalbuminemia as risk factor of wound healing in diabetic foot: a study from tertiary hospital in South India. *Int Surg J*. 2017;4(9):3141-3145.
- Choi SK, Kim CK, Jo DI, et al. Factors associated with a prolonged length of hospital stay in patients with diabetic foot: a single-center retrospective study. *Arch Plast Surg*. 2017;44(6):539-544.
- Volaco A, Chantelau E, Richter B, Luther B. Outcome of critical foot ischaemia in longstanding diabetic patients: a retrospective cohort study in a specialised tertiary care centre. *Vasa*. 2004;33:36-41.
- Lipsky BA, Sheehan P, Armstrong DG, Tice AD, Polis AB, Abramson MA. Clinical predictors of treatment failure for diabetic foot infections: data from a prospective trial. *Int Wound J*. 2007;4:30-38.
- Flores Rivera AR. Risk factors for amputation in diabetic patients: a case-control study. *Arch Med Res*. 1998;29:179-184.
- AlGoblan AS, Alrasheedi IM, Basheir OH, Haider KH. Prediction of diabetic foot ulcer healing in type 2 diabetic subjects using routine clinical and laboratory parameters. *Res Rep Endocr Disord*. 2016;6:11-16.
- Nerone VS, Springer KD, Woodruff DM, Atway SA. Reamputation after minor foot amputation in diabetic patients: risk factors leading to limb loss. *J Foot Ankle Surg*. 2013;52(2):184-187.

24. O'Connor DJ, Gargiulo NJ III, Jang J. Hemoglobin A1c as a measure of disease severity and outcome in limb threatening ischemia. *J Surg Res.* 2012;174(1):29-32.
25. Nather A, Bee CS, Huak CY, et al. Epidemiology of diabetic foot problems and predictive factors for limb loss. *J Diabetes Complications.* 2008;22:77-82.
26. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med.* 2004;141:421-431.

How to cite this article: Gülcü A, Etli M, Karahan O, Aslan A. Analysis of routine blood markers for predicting amputation/re-amputation risk in diabetic foot. *Int Wound J.* 2020;17:1996–2004. <https://doi.org/10.1111/iwj.13491>