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AN OBSERVATIONAL RESEARCH TO EVALUATE PREDICTING POSSIBILITIES OF DIABETIC FOOT ULCERS THROUGH LABORATORY AND CLINICAL BASELINE PARAMETERS

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Abstract:
Objective: *Diabetic foot ulcer prediction is helpful for disease management and clinicians. The objective of this research is to examine the predicting possibilities of diabetic foot ulcer patients by evaluating laboratory and clinical baseline parameters.*
Patients and Methods: *We carried out this observational research at Jinnah Hospital, Lahore from November 2017 to August 2018 on a total of 574 foot ulcer episodes to evaluate amputation predictors. Patients were followed-up for a period of six months.*
Results: *Osteomyelitis, Limb ischemia, gangrene and ulcer depth were determined with the help of Wagner Classification. These were major predictors of overall amputations and major amputations. Older age, coronary artery disease, ulcer size and smoking were also associated with both overall amputations and major amputations. Baseline acute phase reactants levels (polymorphonuclear leukocyte count, white blood cell count, erythrocyte sedimentation rate (ESR), platelet count, albumin and serum C-reactive protein (CRP)) and reduced levels of haemoglobin were associated with the risk of amputation. It was learned through multivariate analysis that increase of one standard deviation in ESR & CRP baseline levels predicted both overall amputations and major amputations.*
Conclusions: *Limb ischemia, local gangrene, diffuse gangrene, osteomyelitis and ulcer depth independently predict amputation. Baseline parameters of CRP and ESR are helpful for amputation prediction for the clinicians.*
Keywords: *Amputation, Acute Phase Reactants, Diabetes, Ischemia, Foot Ulcer and Osteomyelitis.*

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INTRODUCTION:

Diabetic foot ulcers primarily lead to an onset of lower extremity amputations [1]. The frequency of foot ulcers in the lifetime of a diabetic patient is 15% requiring lower extremity amputation [2]. The lower extremity amputation risk is 15 to 45 times more in diabetes [1, 3, 4]. Non-adhering diabetic patients who fail to maintain the level of blood glucose are at serious risk of lower limb disability [1]. Repeated ulceration risk factors include altered foot sensation, trauma, foot deformities, previous foot ulcer, peripheral arterial occlusive disease or amputation [5, 6]. Data about the amputation prediction is very much limited, even in the well-defined state of ulcer development. Ulcer depth, ischemia, the severity of infection, gangrene and osteomyelitis are major predictors of diabetic foot ulcer amputation. Other factors of amputation are older age, macrovascular co-morbidities and microvascular co-morbidities [1, 5, 7 – 9].

Diabetic foot ulcer treatment includes vascular status assessment, infection identification, osteomyelitis identification, surgical debridement, antibiotic therapy, minimal amputation and metabolic control [2, 10]. Clinicians need to know the association of different laboratory and clinical outcomes associated with poor outcomes among such cases also known as amputations. Diabetic foot ulcer prediction is helpful for disease management and clinicians. The objective of this research is to examine the predicting possibilities of diabetic foot ulcer patients by evaluating laboratory and clinical baseline parameters.

PATIENTS AND METHODS

We carried out this observational research at Jinnah Hospital, Lahore from November 2017 to August 2018 on a total of 574 foot ulcer episodes to evaluate amputation predictors. Patients were followed-up for a period of six months. In case of development of new ulcers after healing of previous ulcers were classified as new episodes of ulcer. Due to variable follow-up routine, we followed-up a total of 574 ulcers. Patients were asked for informed consent and hospital ethical permission was also taken before the commencement of research. Patients were briefed about the protocols of this research.

We collected data about various characteristics, smoking status, medical history and physical assessment. The largest diameter and site of the ulcer was documented. Wagner classification was used for the classification of foot lesions. Few selected ulcers also underwent MRI of extremity. Levels of haemoglobin, baseline glycosylated haemoglobin (A1c), liver function tests and kidney test were also carried out. All those patients who presented reduced or absent pedal pulses or ABI (< 0.9) experienced Doppler assessment. Revascularization procedure was also carried out for all those patients who presented vascular insufficiency on requirement basis. All those patients who were planned for angioplasty and vascular surgery were examined through MRI angiography. Patients were also assessed for neuropathy and detailed assessment was also conducted on a need basis.

Routine treatment consisted of bed rest, daily wound care, avoiding putting pressure while ambulating on the affected area, debridement, parenteral antibiotics, minor amputation and major amputation. Above ankle joint amputation was taken as major amputation. Regular wound debridement was also carried out in order to remove necrotic tissue and extensive callus. Skin grafting was carried out on a requirement basis. Antibiotics were given on specialist advice to the patients of infected diabetic foot ulcers. Parenteral treatment was continued after taking culture specimens. During follow-up, the alteration in the antimicrobial regimen was suggested on the basis of clinical and culture outcomes. Prolonged oral treatment preceded parenteral antibiotic therapy. Statistical analysis of the outcomes was made through logistic regression test, One-Way ANOVA and SPSS (P-Value < 0.05).

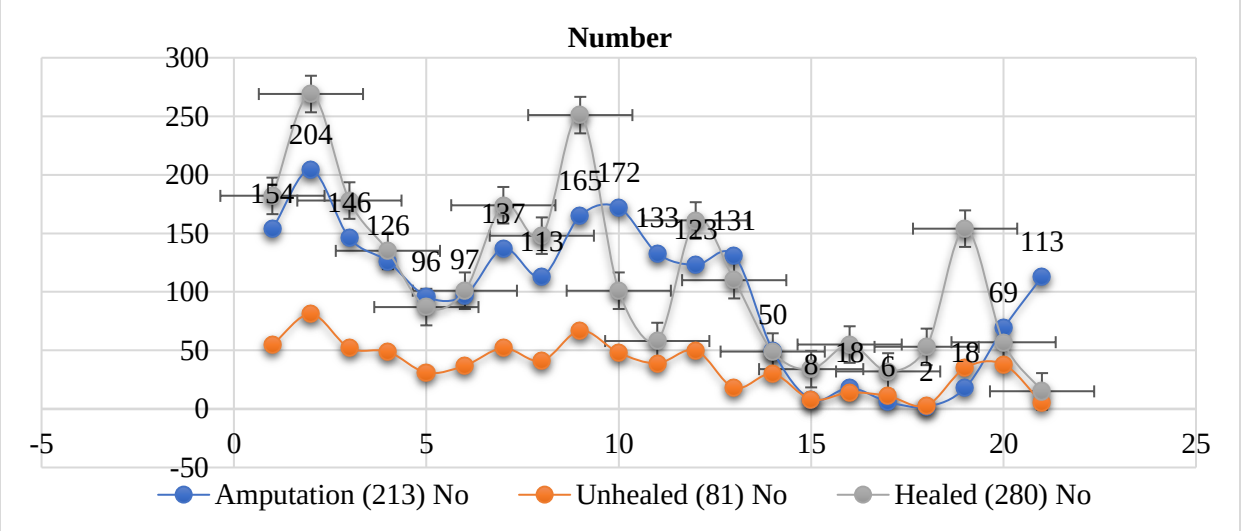
RESULTS:

Osteomyelitis, Limb ischemia, gangrene and ulcer depth were determined with the help of Wagner Classification. These were major predictors of overall amputations and major amputations. Older age, coronary artery disease, ulcer size and smoking were also associated with both overall amputations and major amputations. Baseline acute phase reactants levels (polymorphonuclear leukocyte count, white blood cell count, erythrocyte sedimentation rate (ESR), platelet count, albumin and serum C-reactive protein (CRP)) and reduced levels of haemoglobin were associated with the risk of amputation. It was learned through multivariate analysis that increase of one standard deviation in ESR & CRP baseline levels predicted both overall amputations and major amputations. Detailed outcomes analysis is given in the tabular and graphical data.

Baseline characteristics were recorded in number and percentage for amputation, healed and unhealed ulcers with Diabetes Type, Insulin Use, Hypertension, Coronary Artery Disease, Smoking, Retinopathy, Nephropathy, Neuropathy, Limb Ischemia, Osteomyelitis, Right Foot Ulcer, Toe Ulcer, Fore-Foot Ulcer, Mid-Foot Ulcer, Hind-Foot Ulcer, Leg Ulcer and Wagner Classification (Table – I).

Table – I: Baseline Characteristics of Patients

Average Values	Amputation (213)		Unhealed (81)		Healed (280)		Total (574)	
	No	%	No	%	No	%	No	%
Males	154	72.3	55	67.9	182	65	391	68.1
Type - II Diabetes	204	95.8	81	100	269	96.1	554	96.5
Previous Insulin Use	146	68.5	52	64.2	178	63.6	346	65.5
Hypertension	126	59.2	49	60.5	135	48.2	310	54
Coronary Artery Disease	96	45.1	31	38.3	87	31.1	214	37.3
Smoking	97	45.5	37	45.7	101	36.1	235	40.9
Retinopathy	137	64.3	52	64.2	174	62.1	363	63.2
Nephropathy	113	53.1	41	50.6	148	52.9	302	52.6
Neuropathy	165	77.5	67	82.7	251	89.6	483	84.1
Limb Ischemia	172	80.8	48	59.3	101	36.1	321	55.9
Osteomyelitis	133	62.4	39	48.1	58	20.7	230	40.1
Right Foot	123	57.7	50	61.7	161	57.5	334	58.1
Toe Ulcer	131	61.5	18	22.2	110	39.3	259	45.1
Fore-Foot Ulcer	50	23.4	30	37	49	17.5	129	22.5
Mid-Foot Ulcer	8	3.8	8	9.9	34	12.1	50	8.7
Hind-Foot Ulcer	18	8.4	14	17.3	55	19.6	87	15.1
Leg Ulcer	6	2.9	11	13.6	32	11.5.	49	8.6
Wagner Score - I	2	0.9	3	3.7	53	18.9	58	10.1
Wagner Score - II	18	8.5	35	43.2	154	55	207	36.1
Wagner Score - III	69	32.4	38	46.9	57	20.4	164	28.6
Wagner Score - IV	113	53.1	5	6.2	15	5.4	133	23.2
Wagner Score - V	11	5.2	-	-	1	0.4	12	2.1



Average baseline characteristics were recorded in Mean and SD values for amputation, healed and unhealed ulcers with Age (years), Diabetes duration (years), BMI (kg/m^2), Ulcer diameter (cm), Creatinine (mg/dl), BUN (mg/dl), ALT (U/L), AST (U/L), Hemoglobin (g/dl), WBC (cells/µL), PNL (cells/µL), PLT (cells/µL), Albumin (g/dl), ESR (mm/h), CRP (mg/dl) and A1c (%) (Table – II).

Table – II: Baseline Characteristics of Patients (Mean and SD)

Average Values	Amputation (213)		Unhealed (81)		Healed (280)		Total (574)	
	Mean	±SD	Mean	±SD	Mean	±SD	Mean	±SD
Age (years)	64.6	9.69	62.3	9.05	61.27	11.45	62.65	10.6
Diabetes duration (years)	17.42	9.89	16	8.82	14.63	8.69	15.87	9.26
BMI (kg/m$^{2)}$	25.56	3.73	26.41	4.31	27.26	4.98	26.53	4.53
Ulcer diameter (cm)	5.03	3.85	5.07	4.1	4.19	3.06	4.63	3.55
Creatinine (mg/dl)	1.85	1.61	1.53	1.21	1.62	1.49	1.69	1.51
BUN (mg/dl)	31.12	17.94	27.77	13.94	28.11	16.79	28.19	16.94
ALT (U/L)	20.82	12.18	22.42	20.41	19.37	10.96	20.29	12.95
AST (U/L)	23.17	18.49	24.04	23.11	20.44	18.34	21.92	19.02
Hemoglobin (g/dl)	11.13	1.9	12.14	2.15	11.97	2.02	11.68	2.04
WBC (cells/µL)	12.56	5.55	9.86	3.06	9.84	3.96	10.98	4.73
PNL (cells/µL)	9.95	5.54	6.78	2.74	7.01	3.95	9.13	4.75
PLT (cells/µL)	349.16	112.51	280.89	105.78	304.18	121.83	318.5	118.59
Albumin (g/dl)	3.55	0.54	3.79	0.64	3.91	0.6	3.75	0.61
ESR (mm/h)	73.87	32.41	54.96	29.22	52.75	30.03	61.28	32.39
CRP (mg/dl)	108.76	90.22	35.23	42.35	50.35	70.67	71.45	82.01
A1c (%)	9.02	2.25	8.66	2.18	8.96	2.22	8.94	2.22

Baseline clinical and laboratory factors were recorded for Age, Male (Gender), Type - II DM, Diabetes duration, Previous insulin use, Hypertension, Coronary artery disease, Smoking, Retinopathy, Nephropathy, Neuropathy, Limb ischemia, Osteomyelitis, Ulcer diameter (cm), Gangrene (Wagner Grades 4 & 5), Ulcer depth (Wagner Grade 3 vs. 1 & 2), Creatinine (mg/dl), Hemoglobin (g/dl), WBC (x10^9) cells/L, PNL (x10^9) cells/L, PLT (x10^9) cells/L, Albumin (g/dl), ESR (mm/h), CRP (mg/dl) and A1c (%) (Table – III).

Table – III: Baseline Clinical and Laboratory Factors

Variables	OR	P-Value	95% CI	OR	P-Value	95% CI
Age	1.732	0.018	1.099 – 2.73	1.107	0.75	0.593 – 2.066
Male	1.405	0.071	0.972 – 2.031	1.379	0.227	0.819 – 2.324
Type - II DM	0.746	0.522	0.304 – 1.831	0.97	0.962	0.27 – 3.386
Diabetes duration	1.44	0.159	0.867 – 2.391	1.707	0.094	0.913 3.192
Previous insulin use	1.2	0.317	0.84 – 1.716	1.062	0.809	0.651 – 1.735
Hypertension	1.337	0.094	0.952 – 1.878	1.16	0.533	0.727 – 1.851
Coronary artery disease	1.722	0.002	1.217 – 2.435	1.474	0.104	0.923 – 2.352
Smoking	1.412	0.048	1.003 – 1.986	2.041	0.003	1.278 – 3.257
Retinopathy	1.088	0.638	0.766 – 1.544	1.196	0.473	0.733 – 1.951
Nephropathy	1.06	0.736	0.756 – 1.485	0.939	0.79	0.591 – 1.492
Neuropathy	0.466	0.001	0.296 – 0.732	0.642	0.132	0.360 – 1.144
Limb ischemia	6.174	< 0.001	4.149 – 9.188	13.208	< 0.001	5.652 – 30.866
Osteomyelitis	4.55	< 0.001	3.172 – 6.526	3.632	< 0.001	2.225 – 5.928
Ulcer diameter (cm)	1.595	0.159	0.833 – 3.055	3.976	< 0.001	1.903 – 8.306
Gangrene (Wagner Grades 4 & 5)	23.959	< 0.001	14.043 – 40.878	11.912	< 0.001	7.025 – 20.196
Ulcer depth (Wagner Grade 3 vs. 1 & 2)	7.835	< 0.001	4.622 – 13.283	9.062	< 0.001	3.039 – 27.025
Creatinine (mg/dl)	1.873	0.073	0.943 – 3.719	1.237	0.651	0.492 – 3.112
Hemoglobin (g/dl)	1.843	0.021	1.095 – 3.102	2.266	0.008	1.253 – 4.468
WBC ($x10^9$) cells/L	4.504	< 0.001	2.371 – 8.556	3.357	< 0.001	1.702 – 6.62
PNL ($x10^9$) cells/L	3.388	< 0.001	1.722 – 6.666	1.964	0.126	0.827 – 4.666
PLT ($x10^9$) cells/L	1.803	0.041	1.023 – 3.178	1.54	0.247	0.741 – 3.203
Albumin (g/dl)	2.255	0.007	1.247 – 4.076	2.513	0.01	1.252 – 5.044
ESR (mm/h)	3.871	< 0.001	2.208 – 6.787	5.684	< 0.001	3.058 – 10.568
CRP (mg/dl)	5.25	< 0.001	2.801 – 9.842	3.086	0.001	1.548 – 6.149
A1c (%)	1.106	0.702	0.66 – 1.855	0.706	0.413	0.306 – 1.626

Table – IV: Baseline Values of Acute Phase Reactants

	Overall Amputations	Major Amputations
AUC_{WBC}	0.657	0.657
AUC_{PNL}	0.667	0.689
AUC_{PLT}	0.633	0.661
$AUC_{Albumin}$	0.688	0.709
AUC_{ESR}	0.694	0.715
AUC_{CRP}	0.741	0.708

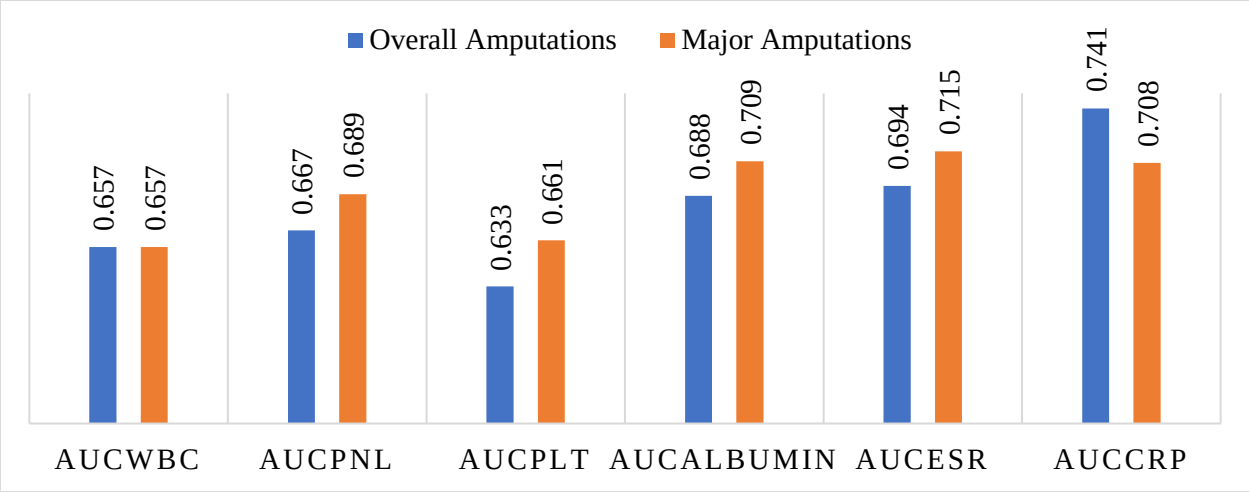


Table – V: Different Cut-Off Values (Overall Amputations Versus Major Amputations)

	Overall Amputations				Major Amputations			
	Sensitivity %	**Specificity %**	**PPV %**	**NPV %**	**Sensitivity %**	**Specificity %**	**PPV %**	**NPV %**
ESR (> 70) mm/h	49.7	76	57.6	69.7	64.3	70.9	27.3	92.1
ESR (> 90) mm/h	31.4	90.1	67.6	66.7	44.6	86.1	35.2	90.2
ESR (> 100) mm/h	20.3	93.1	66	64	26.8	90.3	31.9	87.9
CRP (> 40) mg/dl	69.9	66.2	58.1	76.6	78.3	66.8	22.5	94.2
CRP (> 100) mg/dl	46.6	85.4	71	73.2	50	76.1	25.3	90.4
CRP (> 130) mg/dl	34.6	88.4	66.7	66.8	37	81.8	24.6	88.9

Table – VI: Acute Phase Reactants (Osteomyelitis Versus Non-Osteomyelitis)

	Osteomyelitis (168)		**No Osteomyelitis (218)**		**P-Value**
	Mean	**±SD**	**Mean**	**±SD**	
WBC ($x10^9$) cells/L	11.84	5.26	11.84	5.26	0.001
PNL ($x10^9$) cells/L	9.86	7.59	7.84	5.88	< 0.001
PLT ($x10^9$) cells/L	339.38	121.71	303.11	114.08	0.003
Albumin (g/dl)	3.65	0.59	3.83	0.6	0.004
ESR (mm/h)	72.79	30.25	52.41	31.26	< 0.001
CRP (mg/dl)	106.77	91.23	44.63	62.22	< 0.001

DISCUSSION

We systematically assessed the association between amputation and baseline parameters of acute phase reactants. Important independent overall and major amputation predictors included limb ischemia, gangrene, ulcer depth and osteomyelitis. Limb ischemia and major amputations showed a strong association. Another strong predictor of ulcer outcome was higher Wagner grade. Other associated baseline characteristics were older age, smoking, coronary artery disease and ulcer size. Increased amputation risk also relied on reduced haemoglobin levels and Baseline acute phase reactants levels. The multivariate analysis reflected that baseline ESR and CRP levels independently predicted major and overall amputations.

Previous studies also present osteomyelitis and limb ischemia relation with the increased amputation risk [11 – 13]. Enroth and Diamantopoulos also highlighted limb ischemia as a major associated risk of amputation and foot ulcer infections [14, 15]. Another series reported the relation between amputations and osteomyelitis [16, 17]. According to Armstrong, the amputation risk increases elven times if the wound accesses the bone [18]. With reduced occurrence of osteomyelitis, there was no association between ulcer outcome and infection [19]. Oyibo significantly related amputation risk with Wagner classification [20]. As the ulcers were less in number in Wagner Grade – I; so, we combined both Grades I & II ulcers. According to the outcomes of Wagner Classification, an increased depth of the ulcer independently predicted the risk of amputation.

According to the outcomes of this research, the baseline acute phase reactants values of ESR and CRP were related to the overall outcomes. Velasco also found increased levels of CRP as significant amputation predictor among prolonged patients of diabetes having ischemic foot lesions [20]. Lipsky showed that increased levels of baseline acute phase reactants values (ESR, CRP and WBC) were correlated with the failure of clinical treatment among diabetic foot infections who were managed with antibiotics [21]. Increased amputation risk was also related to reduced serum albumin [22]. Worse clinical outcomes were linked with Leukocytosis among diabetic foot ulcer patients [23]. Increased amputation risk was related with WBC count (> 12.0) cells/µL [24]. Armstrong reported leukocytosis as poor marker of acute osteomyelitis; whereas, the majority of the osteomyelitis cases presented increased levels of ESR [25].

Acute phase response was dependent on severity of infection, osteomyelitis and limb ischemia among diabetic foot ulcer. Clinical data presented increased level of ESR as useful indicator of osteomyelitis. Osteomyelitis probability increases eleven times with an ESR level of (> 70 mm/h) [26]. CRP level was increased in hematogenous osteomyelitis as observed in children; it reduced more rapidly than ESR after proper management which reflects the treatment efficacy having higher sensitivity in comparison to ESR [27]. Peripheral artery disease patients also show an elevated rate of inflammation markers [28].

CONCLUSION

Limb ischemia, local gangrene, diffuse gangrene, osteomyelitis and ulcer depth independently predict amputation. Baseline parameters of CRP and ESR are helpful for amputation prediction for the clinicians.

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