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Prediction of diabetic foot amputation using newly revised DIRECT coding system: Comparison of accuracy with that of five existing classification systems

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Abstract

Diabetes mellitus (DM) causes various complications over time, one such complication is diabetic foot ulcers (DFU), which are challenging to treat and can lead to amputation. Additionally, a system for accurate prediction of amputation has yet to be developed. In total, 131 patients were included in the study after retrospectively collecting data from 2016 to 2020 about DFU. The collected data were used for comparison of the accuracy between five existing classification systems and the newly revised DIRECT coding system, and investigation of risk factors for lower extremity amputation (LEA). The existing five classification systems and DIRECT system can effectively predict LEA. The DIRECT3 system has three elements, C-reactive protein (CRP), ulcer history (UH), and hypertension (HTN) in addition to those of the DIRECT system. It had a high predictive value and accuracy similar to that of Wagner and University of Texas (UT) on depth among the five classification systems. Among the statistically significant risk factors, duration of DM and HTN, haemoglobin (Hb), CRP, and UH showed an association with LEA. The DIRECT coding system is effective for predicting LEA and explaining appropriate treatment methods for DFU, and is widely applicable because of its user accessibility and convenience.

KEYWORDS

amputation, diabetic foot, forecasting, risk factors

Abbreviations: ABI, ankle-brachial index; AUC, area under the curve; BMI, body mass index; CKD, chronic kidney disease; Cr, creatinine; CRP, C-reactive protein; CRP, C-reactive protein; DEPA, depth of the Ulcer, Extent of bacterial colonisation, Phase of ulcer and Association aetiology; DFU, diabetic foot ulcers; DM, diabetes mellitus; DUSS, diabetic Ulcer Severity Score; ESR, erythrocyte sedimentation rate; Glu, glucose; Hb, haemoglobin; HbA1c, glycosylated haemoglobin A; HTN, hypertension; LEA, lower extremity amputation; NPV, negative predictive value; PAD, peripheral artery disease; PPV, positive predictive value; SINBAD, site, ischemia, neuropathy, bacterial infection, and depth score; UH, ulcer history; UT, university of Texas; WBC, white blood cell.

Key Messages

- this is a follow-up study on two articles: article on the comparison of the accuracy of existing DFU classification criteria, and article demonstrating the effectiveness of the DIRECT coding system newly developed by the author
- the purpose of this study was to compare the LEA prediction accuracy of the newly developed DIRECT coding system with those of existing classification systems
- this study also investigated the risk factors leading to LEA based on the data of 131 patients with DFU collected over 5 years
- the DIRECT3 coding system with additional variables such as CRP, UH, and HTN, had the highest sensitivity and NPV values which had the best predictive power among the existing classification systems
- duration of diabetes and HTN, levels of Hb and CRP, and UH were noted as significant risk factors for predicting LEA
- the DIRECT coding system is a classification that not only helps in setting up a treatment policy considering the patient's wounds rather than any other classification method but also makes a diagnosis by examining the patient's general condition

1 | INTRODUCTION

Diabetes mellitus (DM) has a worldwide prevalence of 6.4%.[1] and leads to various complications as the duration of the disease increases. Diabetic foot ulcers (DFU) are one of the most serious complications. Approximately 15%–25% of people with DM have DFU during their lifetime.[2-4] The aetiology of DFU is divided into three categories: neuropathic, neuroischemic, and ischemic with the frequency of each cause being 50%–60%, 20%–30%, and 10%–20%, respectively; diabetic neuropathy accounts for the highest rate of 80%–90%.[5] DFU occurs because of diabetic neuropathy and peripheral vascular disorders.[6] In DFU, even a small wound can inflame the entire foot due to the following reasons: peripheral nerves get damaged resulting in dulled peripheral sensation, ischemia is aggravated due to atherosclerotic changes in the vessel accompanying DM, or bacterial infection resistance is reduced.[7]

In DFU, wounds caused by minor trauma are overlooked or neglected in the early stage resulting in the eventual development of infection or osteomyelitis, which ultimately leads to amputation. Approximately 20% of patients with DFU require lower-extremity amputation (LEA). Of all patients with DM, about 85% of patients with LEA had an ulcer before, and the amputation risk increased with age.[8] In contrast to the upper extremity amputation, LEA causes widespread and comprehensive problems and is expensive. In the case of patients who underwent LEA, it is impossible to estimate the increase in indirect costs such as chronic diseases and socioeconomic costs that occur after amputation, as well as the increase in the direct medical cost required for wound healing several times.[9] In the United States, about 77% of patients aged ≥75 years who underwent amputation were unable to return home after surgery, requiring additional financial assistance and social services.[10]

Currently, various systems are widely used to predict the risk of LEA by simply classifying DFU. However, no prognostic system has been accepted as a standard. We previously conducted a comparative study on the existing classification system of DFU in which we reported that Wagner classification and University of Texas (UT) diabetic wound classification had the highest accuracy in predicting LEA.[11]

The DIRECT coding system was introduced to support the evaluation of various wound conditions and the risk of DFU as well as to provide initial treatment ideas.[12,13] This system consists of six codes, called "DIRECT" by collecting the first letters of each category: debridement of necrosis, infection control, revascularization, exudate control, chronicity, and top surface. The DIRECT system is a wound management interface with a simple and intuitive algorithm (Figure 1). Using the DIRECT system, physicians can recommend an appropriate wound dressing method when setting the wound condition in patients with DFU. (Figure 2).

This study aimed to compare the accuracy of predicting LEA between five representative DFU classification systems and DIRECT system as well as to determine the risk factors associated with LEA. Additionally, this is a follow-up study conducted by the corresponding author

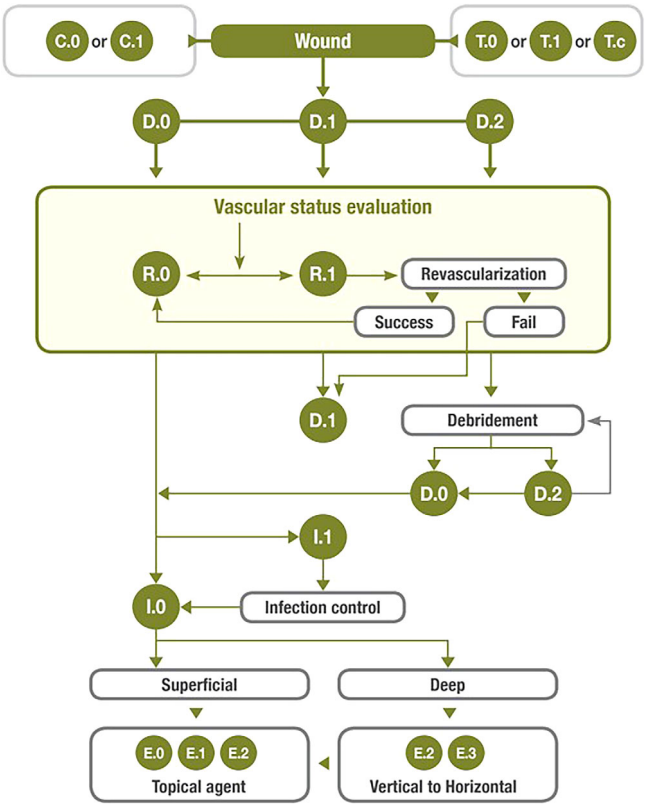

FIGURE 1 Diagnostic algorithm of DIRECT coding system. Adapted from Shin et al. D + WOUND SOLUTION 2014:19[14]

of the paper,[11] which comparatively analysed the accuracy of widely used classification systems of DFU, and the co-author of the paper,[12] which demonstrated the effectiveness of the DIRECT system.

2 | MATERIALS AND METHODS

2.1 | Design

We retrospectively reviewed the records of patients with DFU who received treatment for about 5 years from 2016 to 2020. All patients with DM and active DFU attended our clinic. The term "healing" was defined as complete closure of the DFU without the need for dressing. Minor and major amputations were defined as the upper and lower levels of the ankle joint, respectively. The location of the DFU was classified as toe, forefoot, midfoot, hindfoot, and ankle.

2.2 | Patients

In total, 158 records of patients with DFU were obtained. After excluding patients with dropouts and incomplete clinical databases, 131 patients with DFU were selected for the study.

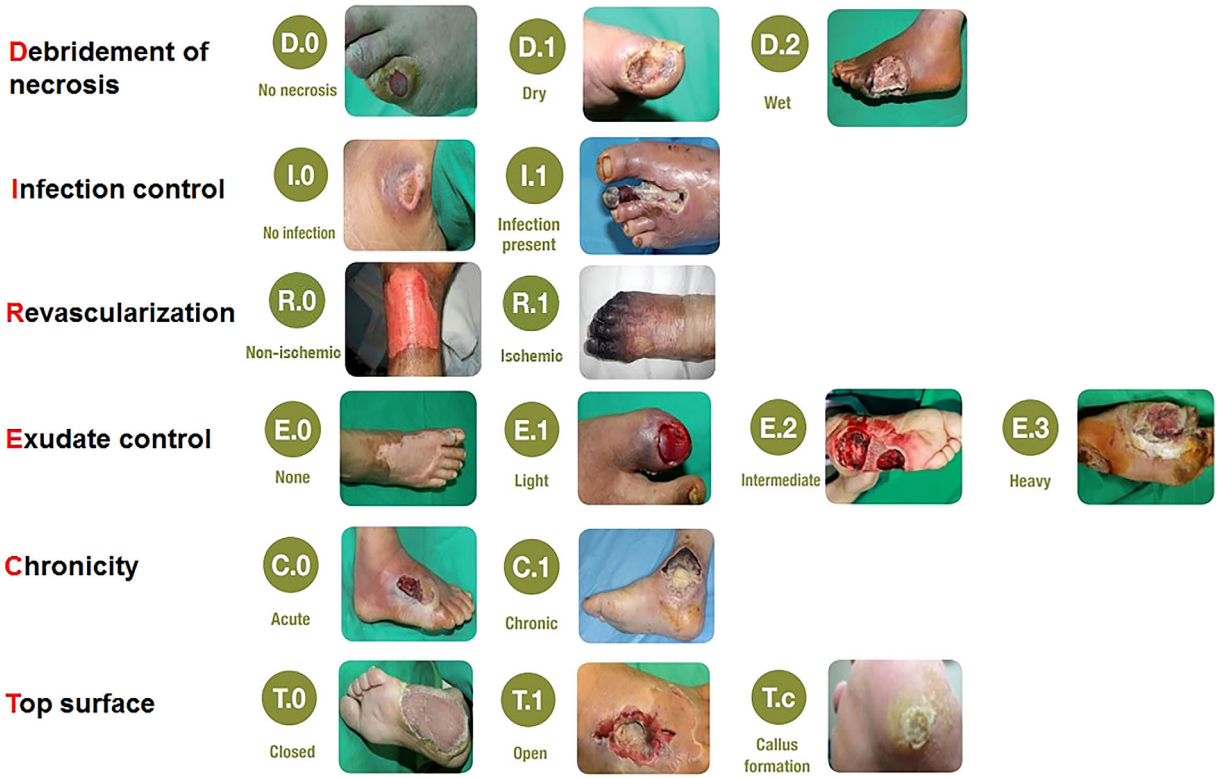

FIGURE 2 Components of the DIRECT coding system

TABLE 1 Baseline Characteristics (continuous variables)

A	Healed ($N = 66$)		Amputation ($N = 65$)		
	Mean	**SD**	**Mean**	**SD**	***P*-value**
Age	58.50	14.65	63.51	10.43	0.0259
Duration of DM	15.55	9.02	19.51	10.16	0.0572
Duration of HTN	7.02	7.78	10.29	8.55	0.0143
BMI	23.50	6.18	22.94	3.02	0.1911
HbA1c[a]	2.07	0.20	2.06	0.18	0.4419
Hb	10.50	1.54	9.73	1.94	0.0107
WBC[a]	8.82	0.98	8.88	1.01	0.3079
Cr	3.61	3.41	4.60	3.86	0.1199
Total Protein	6.50	0.85	6.49	0.90	0.9437
ESR[a]	3.89	0.67	4.02	0.74	0.1245
CRP[a]	−0.31	1.69	0.54	1.62	0.0038

B	Healed ($N = 66$)		Amputation ($N = 65$)		
	N	**%**	***N***	**%**	***P*-value**
Sex					0.9169
Male	38	57.58	39	60.00	
Female	28	42.42	26	40.00	
Ulcer history					0.0156*
No	22	33.33	9	13.85	
Yes	44	66.67	56	86.15	
HTN					0.0079*
No	22	33.33	8	12.31	
Yes	44	66.67	57	87.69	
Retinopathy					0.4283
No	34	51.52	28	43.08	
Yes	32	48.48	37	56.92	
Neuropathy					0.1090
No	27	40.91	17	26.15	
Yes	39	59.09	48	73.85	
Nephropathy					0.4228
No	32	48.48	26	40.00	
Yes	34	51.52	39	60.00	
ABI					<0.0001*
≥0.9	11	19.64	33	70.21	
<0.9	45	80.36	14	29.79	
Location					<0.0001*
Toe	23	34.85	52	80.00	
Forefoot	17	25.76	6	9.23	
Midfoot	6	9.09	7	10.77	

TABLE 1 (Continued)

B					
	Healed ($N = 66$)		Amputation ($N = 65$)		
	N	%	*N*	%	*P*-value
Hindfoot	8	12.12	0	0.00	
Ankle	12	18.18	0	0.00	

Abbreviations: ABI, ankle-brachial index; BMI, body mass index; Cr, creatinine; CRP, C-reactive protein; DM, diabetes mellitus; ESR, Erythrocyte sedimentation rate; Hb, haemoglobin; HbA1c, Glycosylated haemoglobin A; HTN, hypertension; WBC, white blood cell.
[a]Natural logarithmic transformations were performed before analysis.
*P-value <0.05.

2.3 | Risk factor designation

Based on retrospective chart reviews, the following variables were considered: sex; age; medical history including hypertension (HTN) and chronic kidney disease (CKD); diabetic complications including retinopathy, nephropathy, neuropathy; previous ulcer history (UH); body mass index (BMI); infection; and nutritional status. Additionally, laboratory data collected includes: reflect the level of blood glucose, glycosylated haemoglobin A (HbA1c), haemoglobin (Hb), white blood cells (WBC), creatinine (Cr), total protein, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ankle-brachial index (ABI).

These research variables were applied to the DIRECT coding system and five pre-existing classification systems used for LEA prediction. The five classification systems include: (i) diabetic ulcer severity score (DUSS); (ii) University of Texas (UT) diabetic wound classification, (iii) Wagner classification; (iv) depth of ulcer, extent of bacterial colonisation, phase of ulcer healing, and associated aetiology (DEPA) score system; (v) Site, ischemia, neuropathy, bacterial infection, and depth (SINBAD) score.[11]

2.4 | Statistics

This study was performed using the R language ver. 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were compared using the chi-square test, Fisher's exact test, independent *t*-test, univariable logistic regression analysis, and covariate logistic regression analysis. $P < 0.05$ was considered statistically significant.

3 | RESULTS

3.1 | Patient characteristics

Of the 131 recruited patients, 66 healed and 65 underwent LEA. Patients' basic demographics were compared between the two groups. The mean age of the patients was 58.5 years (healed group) and 63.5 years (amputation group). The duration of HTN was significantly shorter in the healed group (7.02 years) than that in the amputation group (10.29 years).

3.2 | Comparison of risk factors

There were no significant differences between the two groups in relation to the following: DM prevalence period, BMI, and male-to-female ratio. The comparison of the laboratory data between the two groups showed no significant differences relative to the levels of: log-transformed HbA1c ($P = 0.4419$), log-transformed WBC ($P = 0.3079$), serum Cr ($P = 0.1199$), total protein ($P = 0.9437$), or log-transformed ESR ($P = 0.1245$). In relation to the healed group, the amputation group had significantly lower and higher levels of Hb ($P = 0.0107$) and log-transformed CRP levels ($P = 0.0038$), respectively. Statistically significant difference in the distribution of DFU locations ($P < 0{\cdot}001$) was observed between the two groups. In the healing group, the sites of DFU were the toe, forefoot, ankle, hindfoot, and midfoot; additionally, the amputation was more strongly associated with toe area (80.6%) than with other locations (Table 1). Table 1A is the result for continuous variables and Table 1B is the result for categorical variables.

We performed covariate logistic regression analysis to confirm the association with the predictor candidates. Age, duration of DM and HTN, Hb, log-transformed CRP, UH, and HTN were statistically significant. We then performed multivariate logistic regression analysis for each DFU classification using these significant variables (Table 2).

3.3 | Comparison of five classification and DIRECT coding systems

The study results were compared with those for five existing classification and DIRECT systems applied to the

algorithm. The five classifications have different scales and standards; therefore, it is difficult to compare them. By reducing the comparative difference between the five systems, statistical corrections were made to classify and group the patients as objectively as possible. As there were no healed patients in the 4-score group of the DUSS system, 4-score group was combined with the DUSS 3-score group (3–4 score group). In the case of Wagner system, as there were no patients in the 0-grade in the amputation group, it was added to the 1-grade (0–1 grade group). As the UT system uses the grade scale on the horizontal axis and stage scale on the vertical axis, it requires two criteria for numbering groups according to severity. Therefore, the UT system was divided into two groups: (i) classification according to the presence of infection (UT on infection) and ischemia and (ii) classification according to wound depth (UT on wound depth). In contrast to the three systems mentioned above, DEPA and SINBAD systems group the scores according to each factor. Therefore, to study the DEPA and SINBAD systems, the patients were divided into three groups according to their severity and complexity: DEPA (low grade: 3–6, moderate grade: 7–9, high grade: 10–12); SINBAD (low grade: 0–2, moderate grade: 3–4, and high grade: 5–6).

The association with LEA was examined by applying the existing DIRECT scoring system and numerical values of this study. D1 grade and D2 grade have different lesion patterns, but they have the same meaning when there is a wound, so they were combined and compared with D0 grade (Table 3). The infection (I) and revascularization (R) categories of DIRECT had

TABLE 3 Logistic regression analysis of components for DIRECT coding system

	OR	Lower CI	Upper CI	*P*-value
Debridement of necrosis (ref: D0)				
D1 and D2	1.849	0.641	5.519	0.2585
Infection (ref: I0)				
I1	8.996	3.399	27.007	<0.0001*
Revascularization (ref: R0)				
R1	11.174	3.736	38.750	<0.0001*
Exudate (ref: E0)				
E1	3.262	0.388	24.598	0.2548
E2	2.154	0.279	14.802	0.4394
E3	4.997	0.463	54.705	0.1791
Chronicity (ref: C0)				
C1	1.434	0.314	7.222	0.6472
Top surface (ref: T0)				
T1	11.109	0.810	319.817	0.0912

Abbreviations: CI, confidence interval; OR, odds ration.
**P*-value <0.05.

TABLE 2 Logistic regression analysis for amputation of risk factor (covariates)

	OR	Lower CI	Upper CI	*P*-value
Age (years)	1.032	1.004	1.062	0.0287
Duration of DM (years)	1.044	1.007	1.085	0.0219
Duration of HTN (years)	1.051	1.007	1.100	0.0262
BMI	0.976	0.904	1.048	0.5083
HbA1c[a]	0.912	0.145	5.704	0.9213
Hb	0.772	0.618	0.947	0.0170
WBC[a]	1.068	0.743	1.617	0.7175
Cr[a]	1.317	0.912	1.917	0.1454
Total protein	0.986	0.662	1.467	0.9432
ESR[a]	1.313	0.803	2.213	0.2865
CRP[a]	1.366	1.105	1.714	0.0050
Sex (ref: female); male	0.905	0.450	1.816	0.7781
UH	3.563	1.498	9.232	0.0056
HTN	3.111	1.338	7.753	0.0106
Retinopathy	1.404	0.706	2.809	0.3341
Neuropathy	1.955	0.940	4.151	0.0756
Nephropathy	1.412	0.708	2.837	0.3289

Abbreviations: BMI, body mass index; CI, confidence interval; Cr, creatinine; CRP, C-reactive protein; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; HTN, hypertension; OR, odds ration; UH, Ulcer history; WBC, white blood cell.
[a]Natural logarithmic transformations were performed before analysis.

TABLE 4 Classification score per group

	Healed ($N = 66$)		Amputation ($N = 65$)		
	N	**%**	***N***	**%**	***P*-value**
DUSS					<0.0001*
0	10	15.15	4	6.15	
1	36	54.55	7	10.77	
2	19	28.79	31	47.69	
3 to 4	1	1.52	23	35.38	
UT on infection					<0.0001*
A	21	31.82	2	3.08	
B	21	31.82	8	12.31	
C	13	19.70	10	15.38	
D	11	16.67	45	69.23	
UT on wound depth					<0.0001*
1	29	43.94	2	3.08	
2	34	51.52	15	23.08	
3	3	4.55	48	73.85	
Wagner					<0.0001*
0 to 1	30	45.45	2	3.08	
2	32	48.48	14	21.54	
3	3	4.55	21	32.31	
4	1	1.52	28	43.08	
DEPA					<0.0001*
3 to 6	32	48.48	4	6.15	
7 to 9	33	50.00	19	29.23	
10 to 12	1	1.52	42	64.62	
SINBAD					<0.0001*
0 to 2	19	28.79	2	3.08	
3 to 4	42	63.64	22	33.85	
5 to 6	5	7.58	41	63.08	
DIRECT 1					<0.0001*
0 to 3	23	34.85	3	4.62	
4 to 6	41	62.12	40	61.54	
7 to 9	2	3.03	22	33.85	
DIRECT 2					<0.0001*
<-2	21	31.82	2	3.08	
-2 to 0	39	59.09	20	30.77	
>0	6	9.09	43	66.15	

Abbreviations: DEPA, depth of the ulcer, extent of bacterial colonisation, phase of ulcer and association aetiology; DUSS, diabetic ulcer severity score; SINBAD, site, ischemia, neuropathy, bacterial infection, and depth score; UT, University of Texas.

*P-value <0.05.

statistically significant results, indicating that they directly affect LEA. To increase the accuracy of results, the DIRECT system was subdivided into DIRECT1 and DIRECT2. The DIRECT1 results were obtained by simply summing the values of each factor, which were divided into three sections similar to other classification criteria: low grade (0–3), moderate-grade (4–6), and high-grade (7–9). On the other hand, DIRECT2 results were obtained by multiplying the values of each factor after finding a constant for each value to maximise the power of

TABLE 5 Logistic regression analysis for amputation in 5 existing classification system

	Univariate				Multivariate			
	OR	**Lower CI**	**Upper CI**	***P*-value**	**OR**	**Lower CI**	**Upper CI**	***P*-value**
DUSS (ref: 0)								
1	0.486	0.120	2.156	0.3175	0.318	0.061	1.756	0.1738
2	4.079	1.184	16.604	0.0330*	2.558	0.532	13.972	0.2519
3 to 4	57.500	8.035	1222.666	0.0006*	64.528	6.549	1676.853	0.0017*
UT on infection (ref: A)								
B	4.000	0.875	28.644	0.1023	4.635	0.838	38.171	0.1024
C	8.077	1.781	58.262	0.0141*	7.914	1.500	63.313	0.0246*
D	42.955	10.575	295.700	<0.0001*	45.619	9.684	352.222	<0.0001*
UT on wound depth (ref: 1)								
2	6.397	1.625	42.759	0.0194*	4.091	0.899	29.382	0.0972
3	232.000	45.452	2024.862	<0.0001*	320.383	48.274	3699.191	<0.0001*
Wagner (ref: 0–1)								
2	6.563	1.651	44.055	0.0183*	4.811	1.074	34.432	0.0630
3	105.000	19.852	933.577	<0.0001*	82.428	11.876	940.168	0.0001*
4	420.000	53.609	10 066.377	<0.0001*	554.290	58.230	15 268.642	<0.0001*
DEPA (ref: 3–6)								
7 to 9	4.606	1.532	17.226	0.0114*	3.924	1.123	17.050	0.0445*
10 to 12	336.000	52.618	6868.671	<0.0001*	271.857	36.826	6081.949	<0.0001*
SINBAD (ref: 0–2)								
3 to 4	4.976	1.283	33.036	0.0418*	6.066	1.213	48.896	0.0484*
5 to 6	77.900	16.737	598.246	<0.0001*	95.263	15.276	968.204	<0.0001*
DIRECT 1 (ref: 0–3)								
4 to 6	7.480	2.367	33.296	0.0021*	7.875	2.197	38.854	0.0038*
7 to 9	84.333	15.772	754.142	<0.0001*	66.132	10.505	679.866	0.0001*
DIRECT 2 (ref: <−2)								
−2 to 0	5.385	1.385	35.790	0.0329*	5.432	1.243	38.809	0.0439*
>0	75.250	16.906	556.594	<0.0001*	65.308	12.938	533.445	<0.0001*

Note: The multivariate analyses were adjusted for age, gender, neuropathy, HTN, ulcer history, and log-transformed CRP.

Abbreviations: CI, confidence interval; DEPA, depth of the ulcer, extent of bacterial colonisation, phase of ulcer and association aetiology; DUSS, diabetic ulcer severity score; OR, odds ration; SINBAD, site, ischemia, neuropathy, bacterial infection, and depth score; UT, university of texas.

*P-value <0.05.

verification ($-6.206 + 0.526 \times D + 2.108 \times I + 2.507 \times R + 0.186 \times E + 0.126 \times C + 2.554 \times T$).

All five classification systems, and DIRECT1 and DIRECT2 systems showed LEA amputation rates and positive trends in stage or grade increase ($P < 0.001$) (Table 4). The multivariate logistic regression analysis showed that a significant increase in LEA occurred with increasing scores of all classification systems. For example, when using the Wagner system, it was noted that the probability of a patient undergoing amputation was 82 times higher in grade 3 than in grade 1 ($P = 0.0001$; OR = 82.428; 95% CI: 11.876–940.168). In grade 4 ($P < 0.0001$; OR = 554.290; 95% CI: 58.230–15 268.642), the probability of a patient undergoing amputation was 554 times more than that in 0–1 grade. When DIRECT1 or DIRECT2 was used, the probability of a patient's amputation at high grade in both methods was similar, approximately 65 times (DIRECT1: $P = 0.0001$; OR = 66.132; 95% CI: 10.505–679.866) (DIRECT2: $P < 0.0001$; OR = 65.308; 95% CI: 12.938–533.445) (Table 5).

The accuracy of these classification systems was examined by calculating sensitivity, specificity, classification accuracy, positive predictive value (PPV), negative predictive value (NPV), and area under the curve (AUC).

TABLE 6 Diagnostic performance of 5 existing classification system and DRIECT system

	Threshold	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC	Lower CI	Upper CI	*P*-value
DUSS	1.5	0.831	0.697	0.763	0.730	0.807	0.804	0.732	0.876	
UT on infection	3.5	0.692	0.833	0.763	0.804	0.733	0.811	0.740	0.882	
UT on depth	2.5	0.738	0.955	0.847	0.941	0.788	0.889	0.837	0.941	
Wagner	2.5	0.754	0.939	0.847	0.925	0.795	0.896	0.845	0.946	
DEPA	8.5	0.785	0.848	0.817	0.836	0.800	0.895	0.842	0.948	
SINBAD	4.5	0.631	0.924	0.779	0.891	0.718	0.856	0.794	0.919	
DIRECT1	5.5	0.662	0.667	0.664	0.662	0.667	0.756	0.679	0.833	
DIRECT2	−0.483	0.846	0.727	0.786	0.753	0.828	0.848	0.783	0.914	
DIRECT3 (+CRP,UH,HTN)	−0.307	0.892	0.773	0.832	0.795	0.879	0.887	0.829	0.944	

Abbreviations: AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; DEPA, depth of the ulcer, extent of bacterial colonisation, phase of ulcer and association aetiology; DUSS, diabetic ulcer severity score; HTN, hypertension; NPV, negative predictive value; PPV, positive predictive value; SINBAD, site, ischemia, neuropathy, bacterial infection, and depth score; UH, ulcer history; UT, university of texas.

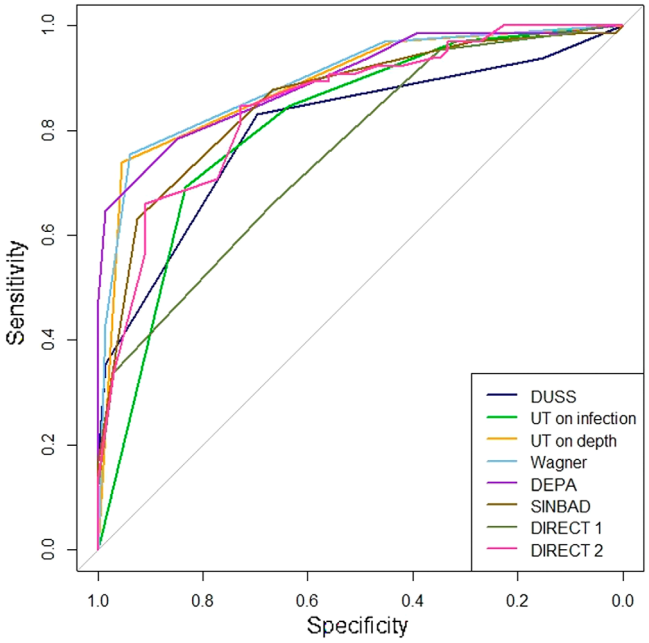

FIGURE 3 ROC curves of the DIRECT algorithm (Including DIRECT1 to 3) and five classification systems. ROC, receiver operating characteristic

PPV is the probability that the patient has a disease when the result is positive and NPV is the probability that the patient does not have disease when the result is negative. Classification with high NPV and PPV was expected to significantly increase the accuracy of LEA prediction. This concept can also be applied to the prediction of LEA occurrence. The UT on wound depth had the highest PPV value (0.941). Both Wagner and UT had the highest accuracy value (0.847) for the depth category. In terms of specificity, the UT on wound depth showed the highest value (0.955). The AUC value was the highest for Wagner (0.896) and DEPA (0.895) (Table 6 and Figure 3). Since the Wagner system obtained overall high values in specificity, accuracy, PPV, and AUC, it can be considered as the most useful tool for the prediction of LEA in patients with DFU.

To increase the predictive power to the same extent as that of the Wagner system, we selected various additional influencing factors, such as CRP, UH, HTN, age, Hb, neuropathy, nephropathy, and duration of DM with constants through covariate logistic regression analysis. Nine additional multiplication formulas were created. Of these, DIRECT3 multiplied the three factors predicted to have the greatest effect: CRP, UH, and HTN ($-8.107 + 0.603 \times D + 1.952 \times I + 2.267 \times R + 0.107 \times E + 0.322 \times C + 2.448 \times T + 0.315 \times \log(CRP) + 0.841 \times (UH) + 1.518 \times HTN$). The accuracy of DIRECT3 classification system was calculated in the same way as above. In relation to DIRECT2, the DIRECT3 had increased sensitivity (0.892; highest value) and NPV (0.879) values. However, the specificity value did not exceed UT on wound depth in any DIRECT method (Table 6 and Figure 3). Thus, the newly devised DIRECT3 had particularly high values for sensitivity and NPV, with an accuracy of 0.832, similar to that of the Wagner system.

4 | DISCUSSION

DFU accounts for a very high proportion of non-traumatic lower extremity injuries worldwide.[15] The Global Lower Extremity Amputation Study Group

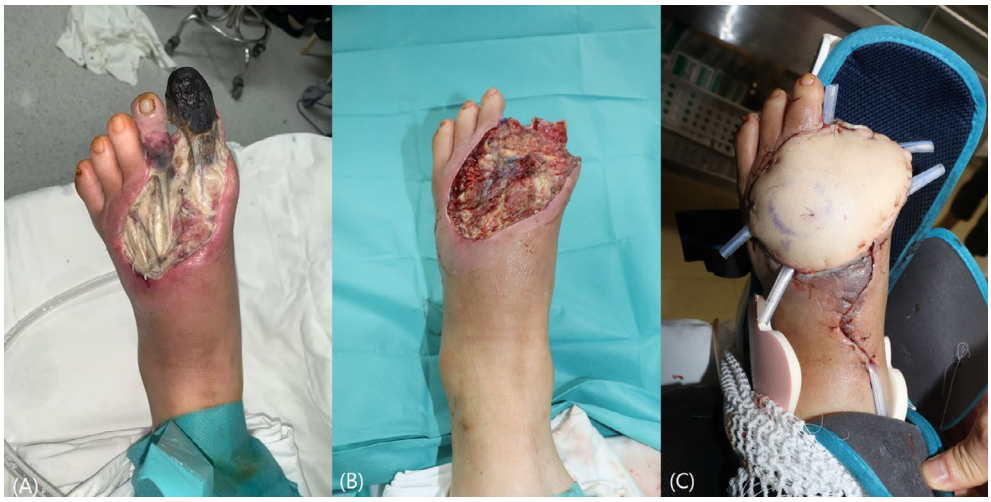

FIGURE 4 Clinical application of DIRECT coding system. A, DFU of the left foot with necrotic tissue in a 61-year-old male. The patient was diagnosed with diabetes and hypertension 20 years ago. According to the DIRECT1 coding system, D2 I1 R1 E3 C1 T1 can be assigned, and a total of 9 points corresponds to a high risk of amputation. On the DIRECT2 system, the result was 2.173, which strongly suggested amputation ($-6.206 + 0.526 \times 1 + 2.108 \times 1 + 2.507 \times 1 + 0.186 \times 3 + 0.126 \times 1 + 2.554 \times 1 = 2.173$). According to the DIRECT3 system, the most highest value was 3.251, and in the end, amputation was performed. ($-8.107 + 0.603 \times 1 + 1.952 \times 1 + 2.267 \times 1 + 0.107 \times 3 + 0.322 \times 1 + 2.448 \times 1 + 0.315 \times \log[27.987\ mg/dL] + 0.841 \times 1 + 1.518 \times 1 = 3.251$). B, Dirty granulation tissue was observed even after debridement and great and second toe amputation. Therefore, angioplasty was performed according to the algorithm of the DIRECT coding system. C, After angioplasty, anterolateral thigh free flap was performed, and limb salvage was successfully performed on 7th day of post-operative days

predicts that 25%–90% of LEAs are related to DM.[16,17] About 15%–27% of DEA require surgical removal of the bone.[18-22] In this study, about 49.6% of patients with DM underwent LEA, about 89.23% underwent minor amputation, and about 10.77% underwent major amputation. Additionally, we noted that DM duration and HbA1c level had no effect on the amputation rate of patients with DM. A study by Tabur et al., showed similar results that duration of DM and HbA1c level had no effect on the amputation rate, in correlation to the amputation rate in 55 patients with type 2 DM.[23] A study by Yesil et al. also revealed that DM duration and HbA1c level were not baseline factors predicting amputation rates.[24] In a study, Miyajima et al. reported no difference in the duration of DM between patients with major amputation and those with minor or no amputations; however, high HbA1c levels were observed in patients with major amputation.[25] In contrast, Adler et al. reported that HbA1c levels were not associated with LEA and the probability of amputation incidence increases with increasing duration of DM.[26] This study was conducted in patients without acute ulceration, and it was noted that both HbA1c levels and the duration of DM may affect LEA in patients without acute ulceration. Based on the study results,[25] it can be considered that HbA1c levels did not affect the amputation rate in the current study because about 89.23% of patients who underwent amputation received minor amputation. In addition, since this study was conducted in patients with acute ulceration, it can be assumed that the duration of DM did not affect amputation.

The known risk factors for LEA in patients with DM include increased CRP levels, HTN, peripheral arterial disease, nephropathy, and neuropathy.[27,28] In this study, the amputation group had lower Hb levels, and higher CRP levels than those in the healed group. Both the groups had similar WBC count and ESR. Other studies have also reported an association between increased CRP levels and LEA in patients with DM. Suzan et al. reported significantly higher WBC and CRP levels in the LEA group.[23] Lipsky et al. also reported that elevated WBC count and CRP and ESR levels contribute to poor clinical prognosis in patients with diabetic foot.[29] Thus, increased CRP level can be considered an important key factor in predicting LEA. However, Eneroth et al. reported that elevated WBC count did not correlate with LEA,[30] indicating increased WBC count alone cannot sufficiently predict LEA.

DFU is the most common precursor of LEA.[31,32] About >60% of patients who underwent LEA had DFU. It has been reported that about 20%–58% of patients with DFU develop another ulcerative lesion within one year of the healing of the prior ulcer.[33] In this study, the UH was significantly associated with the amputation group than the healed group. Therefore, this suggests that the amputation probability is higher in patients with UH.

In this study, according to the univariable logistic regression analysis, the amputation group had more hypertensive patients and longer duration of HTN. Chronic HTN decreases the elasticity of the blood vessel wall and increases its stiffness, which increases the incidence of peripheral artery disease (PAD).[34] In particular, the amputation group showed a significantly higher prevalence of PAD, which is a major risk factor for LEA. If ischemia is caused by a blood circulation disorder and arteriosclerosis, the wound healing is slow, and risk of necrosis increases.[35]

The infection (I) category in DIRECT showed a significant relationship with LEA. This is consistent with the fact that the increased CRP in the existing five classification systems resulted in an increased risk of LEA. Therefore, it is important to manage CRP levels in patients with DFU through active infection control. The revascularization (R) category of DIRECT also had a significant relationship with LEA. Ischemia increases the risk of amputation, and adequate revascularization is required for wound healing. This is consistent with the results of other studies suggesting that the improvement of ischemia through revascularization is directly related to LEA prevention.[13,36]

All five existing classification systems and DIRECT methods showed a positive trend with respect to the increase in the LEA amputation rate in terms of stage or grade ($P < 0.0001$). However, the DIRECT system itself had low verification power, so a weighted system was needed to increase accuracy. Therefore, the newly devised DIRECT3 with three elements CRP, UH, and HTN in addition to those of DIRECT had the best predictive power. DIRECT3 can further improve accuracy by adding CRP, which is a laboratory variable as well as a clinical aspect. These results indicate that DIRECT3 similar to the Wagner system, a widely used diabetic foot classification system, can be effective in predicting the probability of LEA in patients with diabetic foot. In addition, by lowering the score during treatment, the DIRECT system can serve as an indicator to confirm whether the direction of treatment is set properly.

4.1 | Advantages and disadvantages of the DIRECT system

The DIRECT system was developed as a total solution that provides an appropriate treatment method and diagnosis for various wounds. The DIRECT system also addresses physiological points important for wound healing, such as vascular status, whereas other systems focus only on limited wound information.[13] The DIRECT system increased the objectivity by adding laboratory and clinical data such as CRP, UH, and HTN, which is actually the highest predictive value in DIRECT 3 and It has been proven as a result with accuracy.

In addition, the DIRECT coding system has user-friendly design, which provides an understanding of the condition of the wound and suggests the most practical treatment for wound care providers, including less experienced physicians. The DIRECT coding system helps physicians independently make a wound treatment plan for each item.[12] For example, depending on the DIRECT system, a solution may be provided when removal of necrotic tissue or revascularization of the vessel is required. If the other classification is evaluated based on the initial condition of the patient's visit, the DIRECT system re-evaluates the patient's wound improvement or worsening condition, and suggests a treatment method that is changed again according to the algorithm. It can continuously evaluate the patient's condition and treat DFU more accurately.

It is also noteworthy that the importance of revascularization category(R), a category not found in other classifications, was revealed. The highest odds ratio(11.174) of the "R" category proved that improvement in the "R" category with an intervention such as angioplasty had the greatest effect on preventing LEA. Therefore, the vascular status of patients with DM must be evaluated prior to wound healing. If there is stenosis on computed tomography angiography, revascularization with percutaneous transluminal angioplasty or vessel bypass surgery may be required. Based on these advantages, the DIRECT coding system can be widely applied in DFU treatment (Figure 4).

This study has some limitations. Due to the retrospective design, some of the patients' medical information was lost; therefore, the database was not complete, and the patients did not undergo a unified treatment. In addition, as this was a single-institution study there were limits in adding objectivity to the survey results. Further research with a prospective study design targeting multiple centers will increase the accuracy of the DIRECT system. Finally, the factor of osteomyelitis, which is an important factor influencing the treatment of DFU, was not addressed. Research is needed to determine whether osteomyelitis is present through bone scan or magnetic resonance imaging and to systematically add this to the coding system.

4.2 | Conclusion

The DIRECT coding system is a useful tool for predicting the outcomes of DFU and determining treatment methods. In particular, the DIRECT3 system

had an accuracy comparable to that of Wagner and UT on wound depth classification systems. Additionally, the duration of DM and HTN, Hb, CRP, DH, and HTN were found to be statistically significant in predicting LEA.

Through the DIRECT system, it can be suggested that DFU can be properly treated at an early stage, and progression to LEA can be prevented through proper infection control and revascularization.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The study protocol was approved by the institutional review board (IRB number: 2022–02–011-002). All the study procedures were performed in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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REFERENCES

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010;87(1):4-14.
2. Yazdanpanah L, Nasiri M, Adarvishi S. Literature review on the management of diabetic foot ulcer. *World J Diabetes*. 2015;6(1):37-53.
3. Gershater MA, Löndahl M, Nyberg P, et al. Complexity of factors related to outcome of neuropathic and neuroischaemic/ischaemic diabetic foot ulcers: a cohort study. *Diabetologia*. 2009;52(3):398-407.
4. Ikura K, Hanai K, Oka S, et al. Brachial-ankle pulse wave velocity, but not ankle-brachial index, predicts all-cause mortality in patients with diabetes after lower extremity amputation. *J Diabetes Investig*. 2017;8(2):250-253.
5. Yotsu RR, Pham NM, Oe M, et al. Comparison of characteristics and healing course of diabetic foot ulcers by etiological classification: neuropathic, ischemic, and neuro-ischemic type. *J Diabetes Complicat*. 2014;28(4):528-535.
6. 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.
7. Amin N, Doupis J. Diabetic foot disease: from the evaluation of the "foot at risk" to the novel diabetic ulcer treatment modalities. *World J Diabetes*. 2016;7(7):153-164.
8. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation. Basis for prevention. *Diabetes Care*. 1990;13(5):513-521.
9. Claessen H, Narres M, Haastert B, et al. Lower-extremity amputations in people with and without diabetes in Germany, 2008-2012 - an analysis of more than 30 million inhabitants. *Clin Epidemiol*. 2018;10:475-488.
10. Li Y, Burrows NR, Gregg EW, Albright A, Geiss LS. Declining rates of hospitalization for nontraumatic lower-extremity amputation in the diabetic population aged 40 years or older: U.S., 1988-2008. *Diabetes Care*. 2012;35(2):273-277.
11. Jeon BJ, Choi HJ, Kang JS, Tak MS, Park ES. Comparison of five systems of classification of diabetic foot ulcers and predictive factors for amputation. *Int Wound J*. 2017;14(3):537-545.
12. Jun YJ, Shin D, Choi WJ, et al. A Mobile application for wound assessment and treatment: findings of a user trial. *Int J Low Extrem Wounds*. 2016;15(4):344-353.
13. Jun D, Kwon Y, Bae J, et al. Using DIRECT wound assessment to predict limb salvage and provide prognosis of diabetic foot ulcers. *J Wound Manag Res*. 2021;17(1):9-18.
14. Shin DH, Choi HJ, Hong JP, et al. Indications and the d-+wound solution. In: Lee AY, ed. *D+Wound Solution*. 1st ed. Seoul Korea: CGBio Inc.; 2014:12-134.
15. Fitzgerald O'Connor EJ, Vesely M, Holt PJ, Jones KG, Thompson MM, Hinchliffe RJ. A systematic review of free tissue transfer in the management of non-traumatic lower extremity wounds in patients with diabetes. *Eur J Vasc Endovasc Surg*. 2011;41(3):391-399.
16. Li X, Xiao T, Wang Y, et al. Incidence, risk factors for amputation among patients with diabetic foot ulcer in a Chinese tertiary hospital. *Diabetes Res Clin Pract*. 2011;93(1):26-30.
17. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. *Lancet*. 2005;366(9498):1719-1724.
18. Ramsey SD, Newton K, Blough D, et al. Incidence, outcomes, and cost of foot ulcers in patients with diabetes. *Diabetes Care*. 1999;22(3):382-387.
19. Oyibo SO, Jude EB, Tarawneh I, et al. The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. *Diabet Med*. 2001;18(2):133-138.
20. Unwin N. Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia. *Br J Surg*. 2000;87(3):328-337.
21. Apelqvist J, Larsson J, Agardh CD. Long-term prognosis for diabetic patients with foot ulcers. *J Intern Med*. 1993;233(6):485-491.
22. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth,

infection, and ischemia to risk of amputation. *Diabetes Care*. 1998;21(5):855-859.
23. Tabur S, Eren MA, Çelik Y, et al. The major predictors of amputation and length of stay in diabetic patients with acute foot ulceration. *Wien Klin Wochenschr*. 2015;127(1–2):45-50.
24. Yesil S, Akinci B, Yener S, et al. Predictors of amputation in diabetics with foot ulcer: single center experience in a large Turkish cohort. *Hormones (Athens)*. 2009;8(4):286-295.
25. Miyajima S, Shirai A, Yamamoto S, Okada N, Matsushita T. Risk factors for major limb amputations in diabetic foot gangrene patients. *Diabetes Res Clin Pract*. 2006;71(3):272-279.
26. Kanaya AM, Adler N, Moffet HH, et al. Heterogeneity of diabetes outcomes among asians and pacific islanders in the US: the diabetes study of northern California (DISTANCE). *Diabetes Care*. 2011;34(4):930-937.
27. Hennis AJ, Fraser HS, Jonnalagadda R, Fuller J, Chaturvedi N. Explanations for the high risk of diabetes-related amputation in a Caribbean population of black african descent and potential for prevention. *Diabetes Care*. 2004;27(11):2636-2641.
28. Nather A, Bee CS, Huak CY, et al. Epidemiology of diabetic foot problems and predictive factors for limb loss. *J Diabetes Complicat*. 2008;22(2):77-82.
29. Lipsky BA, Senneville É, Abbas ZG, et al. Guidelines on the diagnosis and treatment of foot infection in persons with diabetes (IWGDF 2019 update). *Diabetes Metab Res Rev*. 2020;36(Suppl 1):e3280.
30. Eneroth M, Apelqvist J, Stenström A. Clinical characteristics and outcome in 223 diabetic patients with deep foot infections. *Foot Ankle Int*. 1997;18(11):716-722.
31. Bergin SM, Wraight P. Silver based wound dressings and topical agents for treating diabetic foot ulcers. *Cochrane Database Syst Rev*. 2006;1:Cd005082.
32. Dowd SE, Wolcott RD, Sun Y, McKeehan T, Smith E, Rhoads D. Polymicrobial nature of chronic diabetic foot ulcer biofilm infections determined using bacterial tag encoded FLX amplicon pyrosequencing (bTEFAP). *PLoS One*. 2008;3(10):e3326.
33. Shahi SK, Kumar A, Kumar S, Singh SK, Gupta SK, Singh T. Prevalence of diabetic foot ulcer and associated risk factors in diabetic patients from North India. *J Diabetic Foot Complications*. 2012;4(3):83-91.
34. Husmann M, Jacomella V, Thalhammer C, Amann-Vesti BR. Markers of arterial stiffness in peripheral arterial disease. *Vasa*. 2015;44(5):341-348.
35. Bentzon JF, Otsuka F, Virmani R, Falk E. Mechanisms of plaque formation and rupture. *Circ Res*. 2014;114(12):1852-1866.
36. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Harkless LB, Boulton AJ. A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. *Diabetes Care*. 2001;24(1):84-88.

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