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ORIGINAL ARTICLE

Association of time in range with postoperative wound healing in patients with diabetic foot ulcers

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Abstract

Time in range (TIR) is a novel indicator of glycaemic control that has been reported to have an association with diabetic complications. The objective of the study was to explore the association of TIR with postoperative wound healing in patients with diabetic foot ulcers (DFUs). We retrospectively analysed the data of DFU patients who had undergone surgical treatment from 2015 to 2019. A 1:1 ratio in propensity score matching (PSM) was adopted to compare patients with TIR ≥50% with those <50%. Data were summarised using chi-squared, Fisher's exact, and Mann-Whitney U tests. Patients with TIR <50% underwent a higher rate of secondary surgery within a month ($P = .032$) and had a longer hospital stay ($P = .045$) with greater hospital charges ($P < .001$) than the TIR ≥50% group. Multivariate analysis revealed that TIR ($P = .034$), Wagner score ($P = .009$), diabetes treatment ($P = .006$), and type of surgery ($P = .013$) were independent risk factors for secondary surgery. Additionally, patient subgroups with TIR <50% and baseline HbA1c $< 7.5\%$ ($P = .025$), albumin level ≥ 30 g/L ($P = .039$), HDL < 1.16 ($P = .021$), or Wagner score ≥ 3 ($P = .048$) also experienced a higher incidence of secondary surgery. TIR was correlated with postoperative wound healing in patients with DFUs. Strict glycaemic targets should be established for surgical patients.

KEYWORDS

diabetic foot ulcers, surgery, time in range, wound healing

Key Messages

- time in range is a novel indicator of glycaemic control, as it is strongly linked to physical health and quality of life in patients with diabetes
- we used a propensity score matching method to examine the association between TIR and postoperative wound healing in patients with diabetic foot ulcers (DFUs). In addition, subgroup analysis was performed for relevant factors

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- time in range was correlated with postoperative wound healing in patients with DFUs, and strict glycaemic targets should be devised for patients with DFUs

1 | INTRODUCTION

The treatment of diabetes is a major global public health challenge, with more than 415 million individuals affected worldwide in 2015, the trend of which is increasing numbers, estimated at 642 million in the next 20 years.[1] Diabetes mellitus affects virtually all systems of the body and can lead to nephropathy, retinopathy, and diabetic foot ulcers (DFUs),[2] a complication characterised by vascular lesions, neuropathy, arthropathy, and increased susceptibility to infections.[3,4] It is estimated that up to 15% of people with diabetes will develop foot ulcers at some point in their life.[5] DFUs not only result in a significant personal financial burden, they also impair quality of life and are associated with high levels of amputation and high mortality.[6,7] Surgery is now a conventional therapy for severe DFUs. Because of poor wound healing, patients with DFUs frequently require multiple surgical interventions.

Good glycaemic control is critical for the prevention of diabetes and its complications. Maintenance of normoglycaemia or near-normoglycaemic blood glucose levels can minimise the risk of diabetic complications.[8] Haemoglobin A1c (HbA1c) is considered the gold standard for the evaluation of glycaemic control since the publication of the results of the Diabetes Control and Complications Trial (DCCT).[9] HbA1c reflects an individual's average level of glycaemia over the preceding 2 to 3 months and represents an important parameter closely related to chronic diabetic complications. However, there are a number of limitations with this measure because it does not accurately reflect acute events (such as hypoglycaemia) or glycaemic variability,[10] instead representing long-term glycaemia. In addition, there are significant individual differences in the relationship between HbA1c and mean glucose level.[11] A previous study found that an HbA1c of 8% could reflect a range of 6.11 to 11.94 mmol/L in mean blood glucose level because the index can be influenced by other factors, such as anaemia or renal failure.[12,13]

As continuous glucose monitoring (CGM) has become more popular, time in range (TIR) may represent a meaningful indicator derived from CGM data that indicate glycaemic control.[14,15] TIR is defined as the percentage of time or the duration that glucose levels are within a target range each day, that target range typically being 3.9 to 10.0 mmol/L.[16] TIR reflects hypoglycaemia events and blood glucose fluctuations that can provide guidance for glycaemic control.[17] The validity of TIR using seven-point testing and the association with risk of development of retinopathy and microalbuminuria in DCCT have been demonstrated.[18] The association between HbA1c and wound healing in DFUs has also been corroborated.[19] However, the significance of TIR for wound healing in patients with diabetes remains unknown. Thus, the objective of the present study was to examine the association between TIR and postoperative wound healing in DFU patients.

2 | MATERIAL AND METHODS

2.1 | Study population

The present study was a retrospective study of patients with DFUs presenting at our hospital from May 2015 to December 2019. All hospitalised patients were managed based on established standards for glucose monitoring and wound treatment. The inclusion criteria were as follows: (a) patients with DFUs; (b) patients with foot ulcers treated surgically. Exclusion criteria were as follows: (a) patients with incomplete medical data; (b) patients with non-type 2 diabetes mellitus; (c) patients unwilling to comply with treatment recommendations; (d) patients with prior history of malignancy or mental disorders; (e) patients with severe metabolic disorders, such as diabetic ketoacidosis or in a hyperglycaemic hyperosmolar state. A total of 347 eligible patients were identified after screening, as described in the flowchart in Figure 1. The study protocol received authorization from the ethics committee of the hospital and complied with the principles of the Declaration of Helsinki. As a retrospective study, written informed consent was not required.

2.2 | Data collection

Patient data were collected from a prospectively collected database and the electronic medical records at the hospital. For each patient, the following clinical information was recorded: (a) patient information, including age, gender, body mass index (BMI), instances of ulceration, prior history of hypertension, lower extremity macroangiopathy, peripheral neuropathy, insulin use, history of smoking and drink, and previous amputations; (b) blood tests prior to surgery, including blood glucose, white blood cell

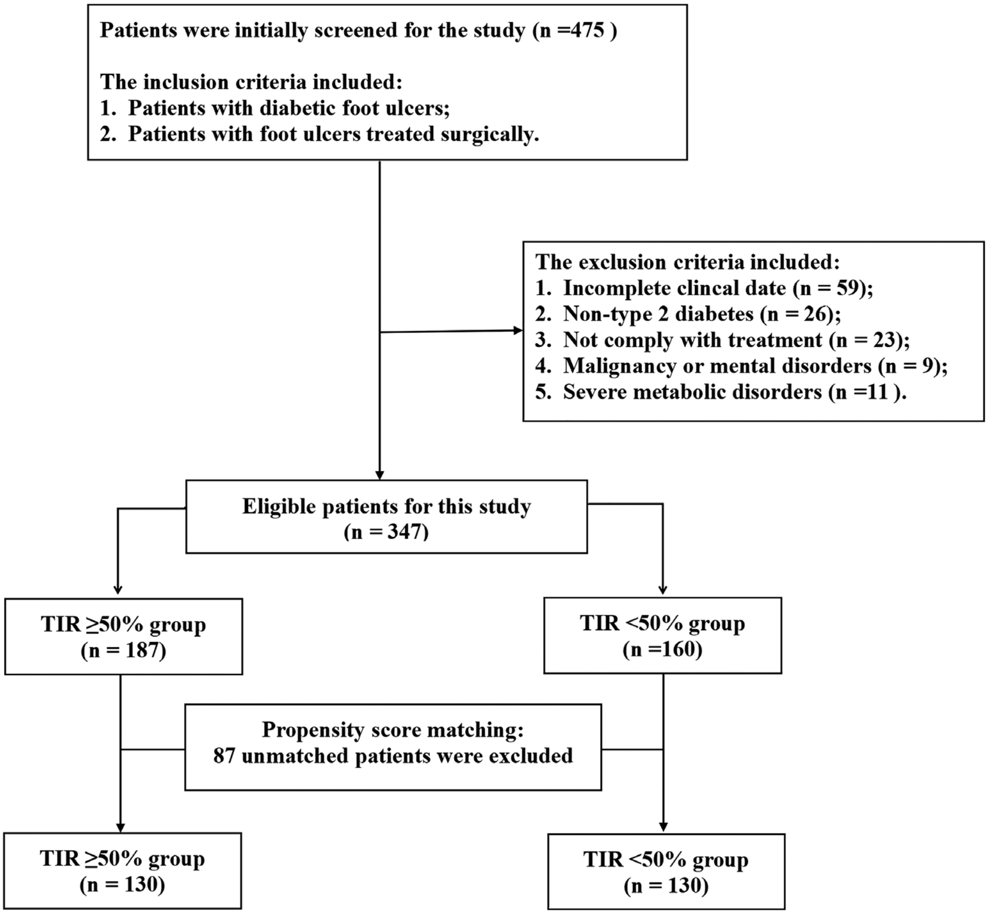

FIGURE 1 Population flowchart. TIR, time in range

(WBC) count, HbA1c value, and haemoglobin, albumin, creatinine, and blood lipid levels; (c) method of surgery; (d) clinical outcomes, including secondary surgery within 1 month, wound conditions at the time of discharge, duration of hospital stay, and hospital costs. Wagner classification scores were determined by reviewing the description of each DFU. The presence of osteomyelitis was also ascertained by clinical and imaging examinations at admission.

2.3 | Glucose monitoring

Inpatients continued to receive their previously prescribed treatment regimens for diabetes. The attending physician reviewed daily glucose measurements and adjusted insulin or other drug doses as required. Additional endocrine consultations could be requested for patients with poor glycaemic control. In addition, blood glucose monitoring was reviewed weekly by a specialist in diabetes.

Seven-point capillary blood glucose values were measured both before and 2 hours after each meal and at bedtime by a diabetes nurse. Glucose levels were recorded in the electronic medical records. Glucose levels were measured using an Accu-Chek Inform II portable glucometer (Roche Diagnostics), which was calibrated as required.

2.4 | Time in range

Glycaemic outcome and performance were reflected in TIR values, calculated for each patient during their hospital stay. TIR values were represented by glucose levels of 3.9 to 10.0 mmol/L and computed for each patient by calculating the percentage of glucose measurements in that range from the number of total measurements (X) and the number within range (Y) as follows: X/Y*100%.

All patients were classified into one of two groups based on whether their TIR value exceeded the predefined threshold *t*. In the present study, a higher threshold value suggests lower tolerance for dysglycaemia. A threshold value of 0.5 was selected as a measure of overall poor glycaemic control in inpatients, whereby the majority of readings exceeded the acceptable glycaemic value of 10 mmol/L. The value of 0.5 has been previously used to correlate the quality of glycaemic control with clinical outcomes.[20] In addition, we conducted a receiver operating characteristic (ROC) curve in the enrolled patients. The values of TIR were plotted into an ROC curve according to secondary surgery (Figure S1), and the optimal cut-off value of TIR was 51.1%. Individuals were therefore placed in either Group I or II for those with TIR ≥50% or <50%, respectively. Hypoglycaemia was defined as at least one blood glucose measurement ≤3.9 mmol/L.

2.5 | Surgical treatment

All patients with DFUs underwent at least one surgery during their hospital stay. Surgery was classified as debridement, minor amputation, or split-thickness skin grafting. Debridement and skin grafts were grouped in the same category because the patient backgrounds are different. The selection of protocol was dependent on wound severity and was chosen by the attending surgeon. The primary outcome measure of the study was whether secondary surgery was performed (as described above) within a month of the initial surgery. Patients received secondary operations after a short period, generally because of poor wound healing or wound infection. Other outcomes included length of hospital stay and cost of hospitalisation. Treatment and care were provided in accordance with the guidelines of the International Diabetic Foot Consensus.[21] The components of wound treatment and care were as follows: (a) formal assessment of ulcer and surrounding skin; (b) provision of any necessary off-loading; (c) debridement or other necessary surgery; (d) appropriate dressing products; (e) appropriate antibiotic therapy; (f) nutrition and self-care.

2.6 | Propensity score adjusted analysis

To minimise the impact of an imbalanced baseline, propensity score matching (PSM) was selected to balance any differences in baseline characteristics of patients between groups. The following factors were treated as covariates for PSM: BMI, preoperative albumin level, WBC count, duration of diabetes, baseline HbA1c, drinker or non-drinker, diabetes treatment, Wagner score, hypertensive status, and type of surgery. PSM was conducted using a 1:1 nearest neighbour matching algorithm and a calliper of 0.2. Clinical outcomes were then evaluated against the statistical measurements.

2.7 | Statistical analysis

Normally distributed continuous data were presented as mean and standard deviation (SD), and non-normally distributed continuous data as median with interquartile range (IQR). Categorical variables were represented as numbers (%). A Student's *t*-test or Mann-Whitney *U* test was performed for continuous data. A chi-square test or Fisher's exact test was performed for categorical variables. The association between variables and outcomes was evaluated using logistic regression. Variables with a *P* value <.10 were selected for subsequent multivariate analysis. Subgroup analysis was conducted using univariate analysis. *P* values <.05 represented a statistically significant difference, and all tests were two-sided. Statistical analyses were conducted using SPSS software (version 22.0; IBM, Armonk, New York, USA), while PSM was calculated using the R version 4.0.3 programming environment.

3 | RESULTS

3.1 | Study cohort

A total of 347 patients with DFUs were eligible for this study from May 2015 to December 2019. Baseline characteristics of the original and matched patients, stratified by TIR, are displayed in Table 1. Prior to matching, the TIR < 50% group had a lower BMI, lower albumin levels, higher WBCs counts, higher baseline HbA1c, a longer history of diabetes, and higher Wagner scores than the TIR ≥50% group, and received insulin treatment. Following matching, 130 patients were included in each group, with baseline characteristics for each group that were well balanced.

3.2 | Clinical outcomes

As indicated in Table 2, of the 260 matched patients, 54 (20.8%) had undergone secondary surgery within a month of initial surgery. Patients in the TIR <50% group exhibited a higher rate of secondary surgery (15.4% vs 26.2%, $P = .032$), longer duration of hospital stay (median, 13.0 days vs 15.5 days, $P = .045$), and higher hospitalisation costs (median, 25 438 yuan vs 32 052 yuan, $P < .001$). There was no difference in in-hospital mortality between groups.

3.3 | Risk factors for secondary surgery

Logistic regression analysis for risk factors associated with secondary surgery is presented in Table 3. In univariate analysis, TIR ($P = .032$), WBC count ($P = .019$), albumin level ($P < .001$), HDL ($P = .005$), Wagner score

TABLE 1 The comparison of patient clinical characteristics before and after propensity score matching

Characteristic	Patients before PSM TIR ≥ 50% group (n = 187)	 TIR < 50% group (n = 160)	 P	Patients after PSM TIR ≥ 50% group (n = 130)	 TIR < 50% group (n = 130)	 P
Sex, n (%)			.125			.602
Female	72 (38.5%)	49 (30.6%)		47 (36.2%)	43 (33.1%)	
Male	115 (61.5%)	111 (69.4%)		83 (63.8%)	87 (66.9%)	
Age, median (IQR), year	67.0 (59.0–75.0)	65.0 (58.0–71.2)	.273	67.0 (58.0–75.0)	65.5 (59.0–72.0)	.449
BMI, median (IQR), Kg/m^2	23.2 (21.2–26.1)	22.9 (20.8–24.5)	.010[a]	22.3 (20.7–25.0)	23.0 (20.9–24.8)	.526
Preoperative serum albumin, median (IQR), g/L	36.8 (32.2–40.2)	32.0 (27.8–36.1)	<.001[a]	34.7 (30.0–38.2)	33.6 (28.9–37.0)	.172
Preoperative haemoglobin, median (IQR), g/L	118.0 (102.5–130.5)	114.0 (99.0–127.0)	.094	118.0 (97.0–129.0)	114.5 (99.0–127.0)	.690
Preoperative WBC count, median (IQR), X10^9/L	7.9 (6.5–10.1)	8.9 (7.1–13.4)	<.001[a]	8.1 (6.5–10.1)	8.3 (6.7–12.2)	.099
Preoperative HDL, median (IQR), mmol/L	0.92 (0.74–1.10)	0.81 (0.70–1.07)	.113	0.90 (0.72–1.06)	(0.71–1.09)	.592
Diabetes duration, median (IQR), years	9.0 (4.0–18.0)	11.0 (8.0–20.0)	<.001[a]	10.0 (5.0–20.0)	10.5(7.0–22.0)	.245
Baseline HbA1c, n (%)			<.001[a]			.206
<7.5%	90 (48.1%)	30 (18.8%)		39 (30.00%)	30 (23.08%)	
≥7.5%	97 (51.9%)	130 (81.2%)		91 (70.00%)	100 (76.92%)	
Drink, n (%)			.037[a]			.572
No	148 (79.1%)	111 (69.4%)		98 (75.4%)	94 (72.3%)	
Yes	39 (20.9%)	49 (30.6%)		32 (24.6%)	36 (27.7%)	
Smoking, n (%)			.361			.576
No	140 (74.9%)	111 (69.4%)		93 (71.5%)	97 (74.6%)	
Yes	47 (25.1%)	49 (30.6%)		37 (28.5%)	33 (25.4%)	
Diabetes treatment, n (%)			<.001[a]			.252
Oral hypoglycaemic	136 (72.7%)	84 (52.5%)		84 (64.6%)	75 (57.7%)	
Insulin	51 (27.3%)	76 (47.5%)		46 (35.4%)	55 (42.3%)	
Wagner score, n (%)			.048[a]			.500
1 to 2	144 (77.0%)	108 (67.5%)		93 (71.5%)	88 (67.7%)	
3 to 5	43 (23.0%)	52 (32.5%)		37 (28.5%)	42 (32.3%)	
Hypertensives, n (%)			.048[a]			.619
No	76 (40.6%)	82 (51.2%)		60 (46.2%)	64 (49.2%)	
Yes	111 (59.4%)	78 (48.8%)		70 (53.8%)	66 (50.8%)	
Lower extremity vascular disease, n (%)			.974			.901
No	95 (50.8%)	81 (50.6%)		63 (48.5%)	64 (49.2%)	
Yes	92 (49.2%)	79 (49.4%)		67 (51.5%)	66 (50.8%)	
Kidney disease, n (%)			.095			.763
No	155 (82.9%)	121 (75.6%)		103 (79.2%)	101 (77.7%)	
Yes	32 (17.1%)	39 (24.4%)		27 (20.8%)	29 (22.3%)	
Peripheral neuropathy, n (%)			.677			.352
No	25 (13.4%)	19 (11.9%)		19 (14.6%)	14 (10.8%)	
Yes	162 (86.6%)	141 (88.1%)		111 (85.4%)	116 (89.2%)	

(Continues)

TABLE 1 (Continued)

Characteristic	Patients before PSM			Patients after PSM		
	TIR ≥ 50% group (n = 187)	TIR < 50% group (n = 160)	P	TIR ≥ 50% group (n = 130)	TIR < 50% group (n = 130)	P
Type of surgery			.005[a]			.210
Debridement/skin grafting	108 (57.8%)	103 (64.4%)		82 (63.1%)	81 (62.3%)	
Minor amputation	60 (32.1%)	29 (18.1%)		32 (24.6%)	24 (18.5%)	
Amputation + skin grafting	19 (10.2%)	28 (17.5%)		16 (12.3%)	25 (19.2%)	

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; IQR, interquartile range; PSM, propensity score matching; WBC, white blood cell.
[a] Statistically significant ($P < .05$).

TABLE 2 Postoperative short-term outcomes

Factors	TIR ≥ 50% group (n = 130)	TIR < 50% group (n = 130)	P
Secondary surgery, n (%)	20 (15.4%)	34 (26.2%)	.032[a]
In-hospital mortality, n (%)	2 (1.5%)	2 (1.5%)	1.000
Hospital stays, median (IQR) (days)	13.0 (10.0-17.0)	15.5(11.0-21.8)	.045[a]
Costs, median (IQR) (yuan)	25 438 (15861-41 974)	32 052 (21094-46 293)	<.001[a]

Abbreviations: IQR, interquartile range; TIR, time in range.
[a] Statistically significant ($P < .05$).

($P = .001$), diabetes treatment ($P = .029$), and type of surgery ($P = .002$) were correlated with secondary surgery. Those factors that were significant were included in the multivariate logistic regression model. TIR ($P = .034$), Wagner score ($P = .009$), diabetes treatment ($P = .006$), and type of surgery ($P = .013$) were confirmed to be independent factors for secondary surgery.

3.4 | Subgroup analysis

As illustrated in Figure 2. Subgroup analyses were conducted to identify potential heterogeneity. Patients with TIR <50% displayed a higher incidence of secondary surgery in the following subgroups: baseline HbA1c <7.5% ($P = .025$), albumin level ≥ 30 g/L ($P = .039$), HDL < 1.16 mmol/L ($P = .021$), and Wagner score ≥3 ($P = .048$). In addition, no significant difference was observed between other subgroups.

4 | DISCUSSION

The incidence of diabetes has continued to increase at an alarming rate worldwide throughout the 21st century, having profound economic and social consequences to public health.[22,23] Inevitably, the rates of diabetic complications have increased, consistent with the increasing numbers of patients with diabetes.[22,24] Therefore, it has become increasingly important to manage diabetes and its associated complications. DFUs are among the most frequent complications of diabetes.[25] DFUs and their adverse consequences, such as amputation, have a serious influence on the health and quality of life of patients.[26] Thus, it is appropriate to identify modifiable factors that could improve wound healing and optimise wound care.

TIR is an intuitively appealing and simple metric, as it is strongly linked to physical health and quality of life in patients with diabetes. A previous report indicated that TIR was inversely correlated with the prevalence of diabetic retinopathy in type 2 diabetes.[27] Additionally, Beck et al[18] found that TIR was significantly correlated with the progression of diabetic retinopathy and microalbuminuria. Their results indicated that the hazard rate for the development of retinopathy and microalbuminuria rose by 64% and 40%, respectively, as TIR reduced by 10%. The studies above suggest that a TIR of 3.9 to 10 mmol/L is an important threshold for patients with diabetes, and has thus attracted increased attention.

As far we know, the present study is the first to report the relationship between TIR and postoperative wound healing in patients with DFUs. Blood glucose values (seven-point testing) of DFU patients were collected during a hospital stay, and TIR values based on the range of 3.9 to 10 mmol/L were recorded for each patient. The

TABLE 3 Univariate and multivariate logistic regression analysis of secondary surgery

Variables	Patients without Secondary surgery ($n = 206$)	Patients with Secondary surgery ($n = 54$)	Univariate analysis *P*	Multivariate analysis *P*
Age, year, median (IQR)	66.0 (58.0–73.0)	66.5 (59.5–74.0)	.335	
BMI	22.8 (20.8–25.0)	22.3 (20.4–24.4)	.780	
Diabetes duration, median (IQR), years	10.0 (6.0–20.0)	10.0 (5.3–20.0)	.796	
WBC count, median (IQR), X10 ^9/L	8.1 (6.5–11.1)	8.8 (7.2–13.1)	.019[a]	0.887
Preoperative serum albumin, median (IQR), g/L	35.1 (30.3–38.1)	31.6 (27.7–33.9)	<.001[a]	0.193
Preoperative haemoglobin, median (IQR), g/L	118.0 (99.0–129.8)	112.5 (97.0–125.0)	.094	0.440
HDL, median(IQR), mmol/L	0.88 (0.74–1.11)	0.74 (0.65–0.95)	0.005[a]	0.315
Baseline HbA1c	8.7 (7.5–10.1)	9.1 (7.2–10.4)	.806	
Hypoglycaemia, n (%)			.636	
0	138 (67.0%)	38 (70.4%)		
1	68 (33.0%)	16 (29.6%)		
Wagner score, n (%)			.001[a]	0.009[a]
1 to 2	153 (74.3%)	28 (51.8%)		
3 to 5	53 (25.7%)	26 (48.2%)		
Diabetes treatment, n (%)			.029[a]	0.006[a]
Oral hypoglycaemic	119 (57.8%)	40 (74.1%)		
Insulin	87 (42.2%)	14 (25.9%)		
Hypertensives, n (%)				
No	99 (48.06%)	25 (46.30%)	.818	
Yes	107 (51.94%)	29 (53.70%)		
Lower extremity vascular disease, n (%)			.849	
No	100 (48.54%)	27 (50.00%)		
Yes	106 (51.46%)	27 (50.00%)		
Kidney disease, n (%)			.544	
No	160 (77.67%)	44 (81.48%)		
Yes	46 (22.33%)	10 (18.52%)		
Type of surgery			.002[a]	0.013[a]
Debridement/skin grafting	139 (67.48%)	24 (44.44%)		
Minor amputation	42 (20.39%)	14 (25.93%)		
Amputation + skin grafting	25 (12.14%)	16 (29.63%)		
Group, n (%)			.032[a]	.034[a]
TIR ≥ 50% group	110 (53.4%)	20 (37.0%)		
TIR < 50% group	96 (46.6%)	34 (63.1%)		

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; IQR, interquartile range; TIR, time in range; WBC, white blood cell.

[a] Statistically significant ($P < .05$).

patients were then categorised into one of two groups, depending on their TIR values. The blood glucose values of patients with DFUs frequently are above 10 mmol/L, or even higher.[28] In our study, the proportion of patients with TIR <70% was 74.6% (257/347), and patients with TIR <50% was 46.1% (160/347), and the mean TIR for the participants was 50.1% ± 16.4%, and the data are similar to previous diabetes studies.[18] The demarcation point of TIR is set to 50% based on ROC curve and the optimal cut-off value. Additionally, it has previously been observed that in patients where 50% of SMBG readings are in such a range, HbA1c would be approximately

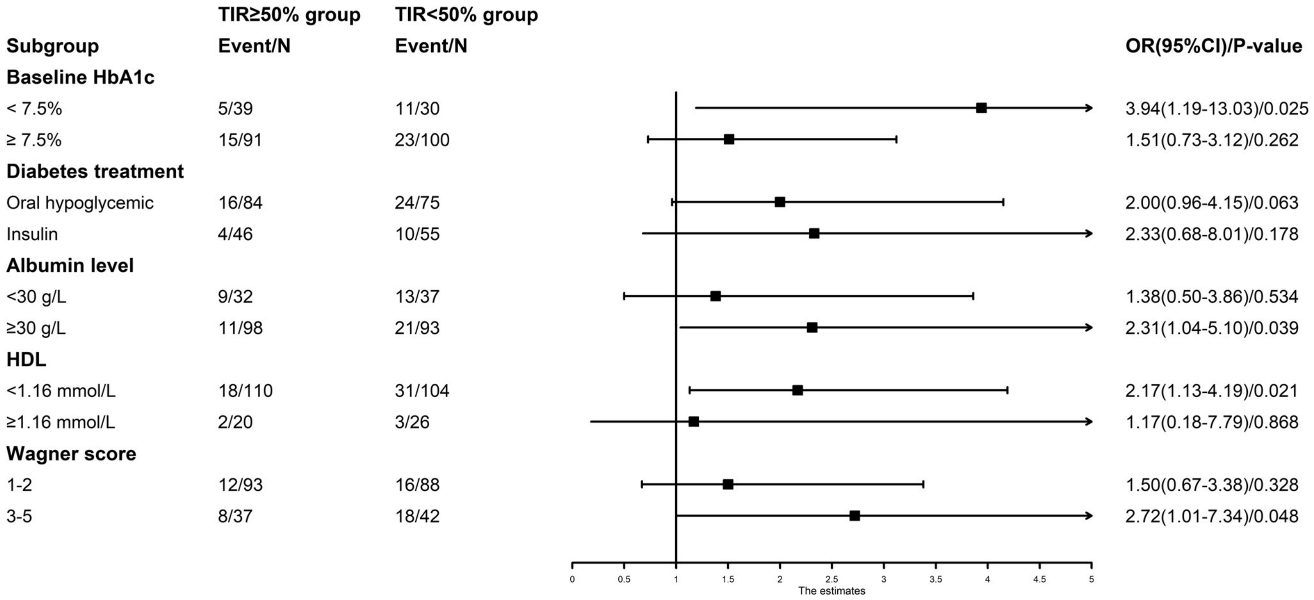

FIGURE 2 Subgroup analysis was conducted to explore the effect of TIR for distinct populations. CI, confidence interval; HDL, high-density lipoprotein; OR, odds ratio; TIR, time in range

7%.[29] The present study implemented PSM to eliminate the bias caused by baseline characteristics and ensure good comparability between groups. Prior to matching, substantial differences in BMI, albumin level, WBC count, duration of diabetes, baseline HbA1c level, whether the patient was a drinker or hypertensive, type of diabetes treatment, Wagner score, and type of surgery were observed between the groups. After matching, the patient characteristics were well balanced between the groups.

In the current study, we demonstrated that there was a statistical difference in the incidence of secondary surgery within a month between the two TIR groups (<50% and ≥50%) in patients with DFUs who had undergone surgery. Patients in the TIR <50% group were at a higher risk of undergoing secondary surgery. Membership of this group predicted negative outcomes for wound healing in DFU patients, which was not associated with haemoglobin A1c values. Numerous physiological factors are considered to influence poor wound healing in patients with hyperglycaemia, which impairs the migration and proliferation of keratinocytes[30] and contributes to increased oxidative stress because of the generation of reactive oxygen species.[31] Hyperglycaemia can stimulate the release of inflammatory factors from monocytes that exacerbate an inflammatory response, thereby affecting the wound healing process.[32] In addition, exposure to high glucose leads to the formation and deposition of advanced glycation end products, demonstrated to be implicated in poor wound healing in diabetic mice.[33] Poor healing or serious wound infections often require secondary surgical intervention, frequently resulting in longer hospital stays with higher costs.

Multivariate logistic regression analysis revealed that Wagner score, diabetes treatment, and type of surgery are also independent risk factors for secondary surgery in patients with diabetes. The Wagner score is an indicator of the severity of DFUs.[34] Advanced Wagner grades were predictive of poor clinical outcomes in patients with DFUs due to a greater number of severe infections and the occurrence of gangrene.[35] Insulin is a synthetic metabolic drug that could theoretically promote wound healing via its influence on protein synthesis, an inflammatory response, and other processes. Different surgical procedures are used because of the corresponding condition of DFU. Amputations and skin grafting tend to result in a larger wound after surgery.

Baseline HbA1c was considered a marker of previous diabetic control and used to stratify patients. Patients with HbA1c <7.5% would be considered to have acceptable glycaemic control, and those ≥7.5% indicative of inadequate control. We found an association between lower TIR and poor wound healing, but it seemed to be more apparent in patients with well-controlled diabetes. This finding is similar to former studies[36,37] in which patients with chronic hyperglycaemia displayed superior tolerance to increased in-hospital glycaemic variation, whereas patients with well-controlled diabetes were more vulnerable to glycaemic variation. It is, therefore, necessary to establish stringent glucose targets for patients with well-controlled diabetes during hospitalisation. This was similarly observed with other subgroups (Figure 2).

Greater attention should be paid to glycaemic changes in such patients.

There are two methods of recording blood glucose values, either by CGM or seven-point SMBG testing. CGM is more accurate for blood glucose monitoring, but more expensive and device-dependent, compared with seven-point testing data.[38] Despite technological advancements in CGM, SMBG using capillary samples remains the main method of measuring glucose level for most patients with diabetes globally.[39-41]

HbA1c is among the most important indicators for the management of diabetes, but it does not reflect alterations in blood glucose over a short period of time. As found in a recent study by Betiel et al,[19] baseline or prospective HbA1c values did not appear to have significant clinical importance for wound healing in patients with DFUs. TIR values provide a full range of blood glucose parameters including hypoglycaemia, acute hyperglycaemia, and blood glucose fluctuations, and compensate for the deficiency of HbA1c values.[14] The present study confirmed that lower TIR values are associated with poor clinical outcomes in DFU patients following surgery. TIR is expected to surpass HbA1c and become a primary evaluation indicator for glycaemic control and management in the future.

There are a number of limitations to this study that should be considered. Firstly, because the numbers of patients with type 1 diabetes were relatively small in the hospital, the study did not include patients with type 1 diabetes in the analysis. Secondly, this study only explored the relationship between TIR and short-term clinical outcomes of patients with DFUs, without an assessment of long-term prognosis. This will be considered in follow-up studies. Thirdly, this was a retrospective study. Although PSM analysis was used, various confounding factors may still have been present. In addition, there are not enough patients with DFUs in the analysis. Therefore, the results should be validated in a multi-centre prospective study.

5 | CONCLUSIONS

The present study demonstrated that patients with TIR <50% were linked to poor wound healing after surgery in DFU patients, especially those with a baseline HbA1c <7.5%. Strict glycaemic targets should be devised for patients with DFUs undergoing surgery, which is beneficial to reduce hospital stay and financial burden for patients.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

AUTHOR CONTRIBUTIONS

Ze-Xin Huang and Sheng Zhao initiated the study design and wrote the manuscript. Hui-Hui Zhang, Ying Huang, and Yu-Ning Ma contributed to the acquisition, analysis, and interpretation of data. Xiao-Qian Chen supervised the study. Sheng-Lie Ye and Ying-Huan Xin revised the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

Data supporting the results presented in the paper are available upon reasonable requests.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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