

Diabetes Complications and Related Comorbidities Impair the Accuracy of FreeStyle Libre, a Flash Continuous Glucose Monitoring System, in Patients with Type 2 Diabetes

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Background: Although flash continuous glucose monitoring systems (FCGM) accuracy has been extensively studied in diabetes, its accuracy is still not fully evaluated in type 2 diabetes (T2D) patients in real-world settings. In the present study, we aim to assess the effects of diabetes complications and related comorbidities on FCGM accuracy in T2D patients with diabetes complications and related comorbidities in the real world.

Methods: FCGM data were collected at eight-time points daily (3 AM, 7 AM, 9 AM, 11 AM, 1 PM, 5 PM, 7 PM, and 9 PM) from 742 patients with T2D and compared with simultaneous fingertip capillary blood glucose (reference blood glucose, REF), and the difference was evaluated using Parkes error grid (PEG), surveillance error grid (SEG), and logistic regression analysis.

Results: In total, 25,579 FCGM/REF data pairs were included in the study. The FCGM values were lower than the paired REF values in 75% of the pairs. The maximum bias (−23.0%) and maximum mean absolute relative difference (24.5%) were observed at 3 AM among eight-time points. SEG analysis also demonstrated the highest percentage of paired readings in moderate and great risk zone (C and D) at 3 AM than PEG analysis (7.33% vs 0.43%, $P < 0.001$). According to the SEG classification, hypoglycemia, infection, diabetic foot, diabetic ketoacidosis, and hypertension were independent risk factors that impaired FCGM accuracy in patients.

Conclusion: FCGM commonly underestimates blood glucose levels. Compared with PEG, SEG analysis seems more conducive to the analysis of FCGM performance. The present data highlights the impairment of diabetes complications and related comorbidities on the FCGM accuracy in T2D patients.

Keywords: flash continuous glucose monitoring system, type 2 diabetes, surveillance error grid, Parkes error grid, diabetes complications

Introduction

Self-monitoring of blood glucose (SMBG) is an integral component of diabetes management that aims to improve glycemic control and decrease the risk of diabetes-related complications.^{1–3} Blood glucose monitoring system (BGMS), including real-time continuous glucose monitoring (CGM) and intermittently scanned CGM (also known as flash continuous glucose monitoring systems, FCGM), can provide continuous measurements of glucose levels and thereby aid diabetes patients in the adjustment of their diet, physical activity, and treatment regimen.^{4,5} Any error in the BGMS, including slight inaccuracies in the measurements, could adversely affect patient care and treatment.^{6,7} CGM measures

the glucose level in the subcutaneous interstitial fluid to estimate blood glucose. Therefore, it is crucial to evaluate the performance and accuracy of CGM based on analytical precision and clinical accuracy.⁸

Unlike real-time CGM, FCGM is designed to measure glucose levels without the need for calibration with blood glucose samples, which improves convenience and quality of life in diabetes patients. The FCGM accuracy has been extensively studied in type 1 diabetes (T1D) and type 2 diabetes (T2D).^{9–12} However, its accuracy remains to be fully explored in T2D, particularly in those with diabetes complications and related comorbidities using emerging analysis. In our previous study, we revealed the accuracy of FCGM reading out of range should be cautiously interpreted, especially as reading below the meter range.¹³ We also reported that T2D patients with hypertension had a higher frequency of readings below the meter range.¹³ In the present study, we aimed to evaluate the effect of diabetes complications and related comorbidities on the performance of FCGM in T2D patients. In addition, two methods for assessing clinical characteristics affecting FCGM accuracy, the Parkes error grid (PEG) and surveillance error grid (SEG), were compared.

Methods

Patients

The paired values of glucose meter and FCGM from 742 adult patients with T2D were analyzed in the present study. All patients were from the Second Affiliated Hospital of Guangzhou Medical University between January 9, 2018, and January 7, 2020. The patients were hospitalized for newly diagnosed or poorly controlled diabetes and were enrolled for using FCGM. Inpatients were ineligible for application of glucose meter and FCGM: 1) if they had shock, unconsciousness, or other conditions that could affect their cooperation in the study, 2) if they had coagulopathy, infectious diseases, or other disorders, in the opinion of the clinicians, would put the patients at risk. This study complied with the Declaration of Helsinki and was performed according to the protocol approved by the academic ethics review boards of the hospital. Informed consents were obtained from all patients. Our study complies with the Declaration of Helsinki.

Data Collection and Analysis/Study Design

The specialist nurses subcutaneously placed a 4–5 mm linear probe (FCGM sensor, FreeStyle Libre, Abbott Diabetes Care) on the outer side of the left upper arm of the patient. The data were collected the day after the sensor installation and the correction of diabetic ketoacidosis. The indicators of correction of DKA included: 1) negative serum and urinary ketones, 2) normal serum electrolytes and serum osmolality, 3) normal arterial blood gases, and 4) reducing blood glucose and correcting syndromes of dehydration. The specialist nurses performed SMBG and scanned the sensor at the same time. All patients were instructed to consume a diabetic diet based on their weight at fixed meal times: 7 AM, 11 AM, and 5 PM. There were no extra meals or strenuous exercise during hospitalization.

The glucose levels in the fingertip capillary blood were measured at eight-time points (3 AM, 7 AM, 9 AM, 11 AM, 1 PM, 5 PM, 7 PM, and 9 PM) using a blood glucose meter (Accu-Chek Performa, Roche) as the reference blood glucose (REF) to compare with FCGM data at the same time point. The consistency and difference between FCGM readings and REF were evaluated using the mean absolute relative difference (MARD), Bias, Bland-Altman plots, PEG, and SEG.

Error Grid Analysis

PEG was constructed according to the recommendations previously reported by DuBois et al¹⁴ and outlined by Pfützner et al.¹⁵ SEG analysis was conducted using the Excel macro program available in R software and the Diabetes Technology Society website (www.diabetestechology.org/SEGsoftware).¹⁶

Statistical Analysis

The Statistical Package for the Social Sciences software (version 22.0) was used to perform all statistical analyses. The Shapiro–Wilk test was performed for assessing the normality of data, and nonparametric statistical tests were used for assessing the non-normality of data. Logistic regression analysis was performed to identify the risk factors that affected FCGM accuracy in patients. $P < 0.05$ indicated statistical significance.

Results

Among the 742 patients included in the study (Table 1), elderly patients aged over 60 years accounted for 62.9% of the total cohort, with a median age of 64 years. Twenty-seven patients (3.6%) had diabetic ketoacidosis (DKA), forty-five patients (6.1%) had diabetic foot, and 277 patients (37.3%) had previous cardiovascular and cerebrovascular events.

Table 1 Clinical Characteristics of Patients (n = 742)

Characteristic	n (%) / Media (quartile)
Age (years)	64 (55, 73)
Gender	
Male	373 (50.3%)
Female	369 (49.7%)
BMI (kg/m²)	24.23 (21.88, 24.23)
Ketone (mmol/L)	0.4 (0.2, 0.6)
Creatinine (umol/L)	77 (62, 99)
Total cholesterol (mmol/L)	4.37 (3.59, 5.25)
HDL cholesterol (mmol/L)	0.99 (0.83, 1.20)
24h microalbuminuria (mg/24h)	156.40 (98.75, 309.75)
Albumin (g/L)	38 (35, 41)
Diabetic nephropathy	
Yes	231 (31.1%)
No	511 (68.9%)
Hypertension	
Yes	395 (53.2%)
No	347 (46.8%)
Cardiovascular and cerebrovascular events	
Yes	277 (37.3%)
No	465 (62.7%)
Insulin dose (U)	31 (0, 50)
Duration (years)	7.00 (1.00, 10.00)
Hyperglycemia	
Yes	178 (24.0%)
No	564 (76.0%)
HbA1c (%)	8.8 (6.9, 11.2)
Hb (g/L)	126 (113, 141)
CO₂CP (mmol/L)	23.9 (22.4, 25.6)
Triglycerides (mmol/L)	1.40 (0.97, 2.09)
LDL cholesterol (mmol/L)	2.70 (1.99, 3.51)
eGFR (mL/min)	84.60 (60.05, 104.50)
Plasma colloid osmotic pressure (mOsm/kg)	284.27 (281.00, 287.79)
Diabetic foot	
Yes	45 (6.1%)
No	697 (93.9%)
Infection	
Yes	180 (24.3%)
No	562 (75.7%)
DKA	
Yes	27 (3.6%)
No	715 (96.4%)
Peripheral vascular disease	
Yes	573 (77.2%)
No	169 (22.8%)

Notes: Data are expressed as n (%) or median (quartile, 25th and 75th percentiles); the definition of hypertension according to European Society of Cardiology/European Society of Hypertension guidelines.

A total of 25,579 paired data in FCGM range from 742 patients were evaluated. The consistency and difference between FCGM readings and REF were evaluated using Bias, Bland-Altman plots, MARD, and CV (Figure 1). The Bland-Altman plots presented a greater error in the lower blood glucose, which gradually decreased as REF increased (Figure 1A); 72.3% of the paired FCGM/REF readings showed FCGM values below REF, even up to 91.5% at the 3 AM time point (Figure 1B). The maximum bias (-23.0%) and maximum MARD value (24.5%) were also observed at the 3 AM time point, which was at least 10% greater than those at other time points (Figure 1C). Moreover, the FCGM accuracy according to the ISO 15197:2013 standard showed the highest percentage (50.0%) of above 20 mg/dL or 20% at 3 AM among eight-time points (Figure 1D).

To optimally assess the accuracy of continuous glucose sensors, PEG and SEG were compared for evaluating the FCGM accuracy by plotting the paired data in the error grids (Figure 2, Supplementary Table 1). In contrast to the clear boundaries of a large range of divisions of PEG, the SEG with 15 color-coded risk levels (Supplementary Table 2) shows the progressive and continuous boundaries between the different strata. SEG analysis showed the significantly higher percentage of paired readings in risk zone C and D than PEG analysis (7.33% vs 0.43% , $P < 0.001$) (Figure 2). We also found the highest proportion of paired readings in SEG risk zone C and D at the 3 AM time point (40.3%) compared with other time points. Of 29 paired readings in SEG risk zone D, only two pairs were in Parkes risk D, three pairs in Parkes risk B, and 24 pairs in Parkes risk C (Supplementary Table 3). Notably, 28 FCGM values of 29 FCGM/REF paired readings in SEG risk zone D were below 70 mg/dL, but all 29 paired REF readings were above 110 mg/dL and 9 of them were above 200 mg/dL, which suggested the severe clinical risk of FCGM may be primarily the false alarm of hypoglycemia.

Then, to analyze the effects of clinical characteristics on FCGM accuracy, the patients were divided into two groups according to whether their paired values included SEG risk zone C/D distribution. Compared to those without risk zone C/D readings, 415 patients (55.9%) with risk zone C/D readings displayed: longer diabetes duration, higher

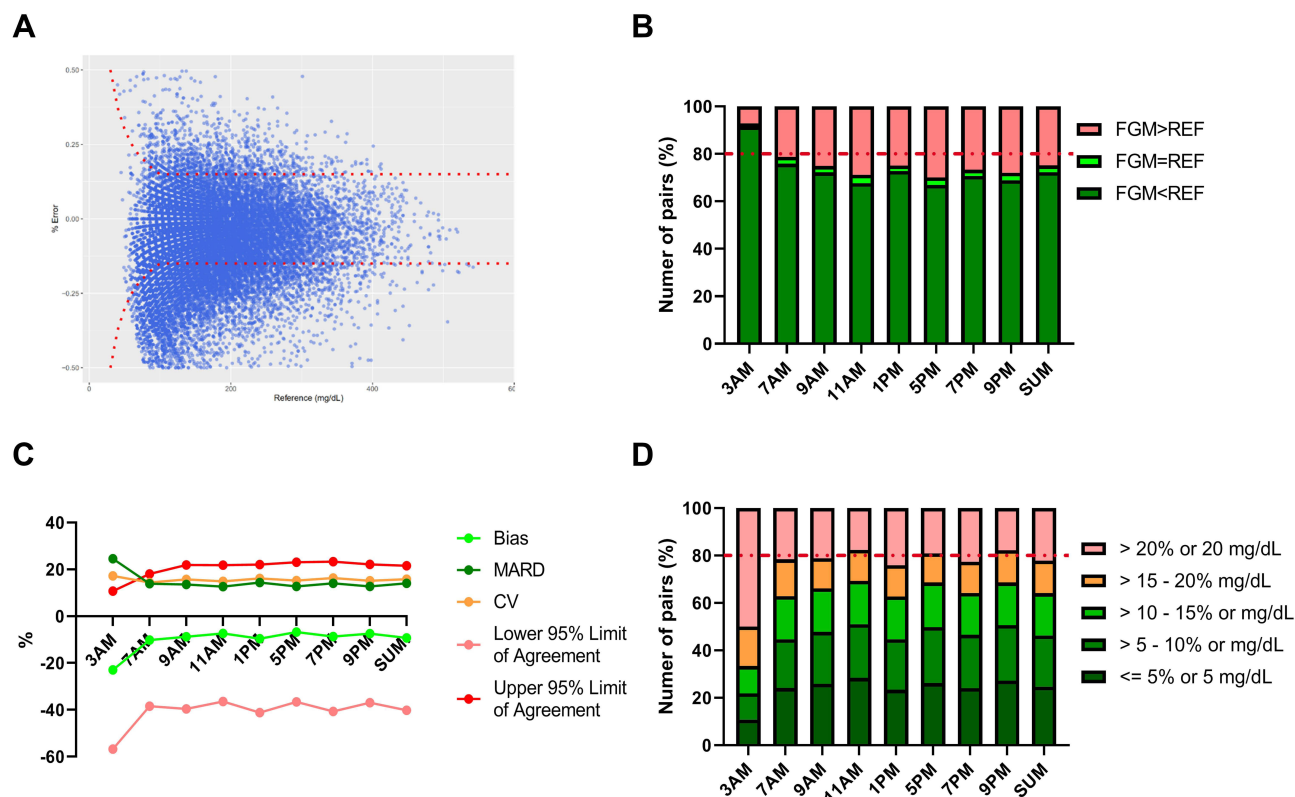


Figure 1 The consistency and difference between FCGM readings and REF in patients. Bland-Altman plots (A); comparison of FCGM value and REF value (B); Bias, MARD, CV, 95% limit of agreement (C); difference according to the ISO 15197:2013 standard (D). Bias: mean relative difference between FCGM and REF (FCGM-REF)/REF; MARD: $|FCGM-REF|/REF$; CV: standard deviation of the relative difference between FCGM and REF. Lower 95% Limit of Agreement: Bias - $1.96 \times CV$; Upper 95% Limit of Agreement: Bias + $1.96 \times CV$.

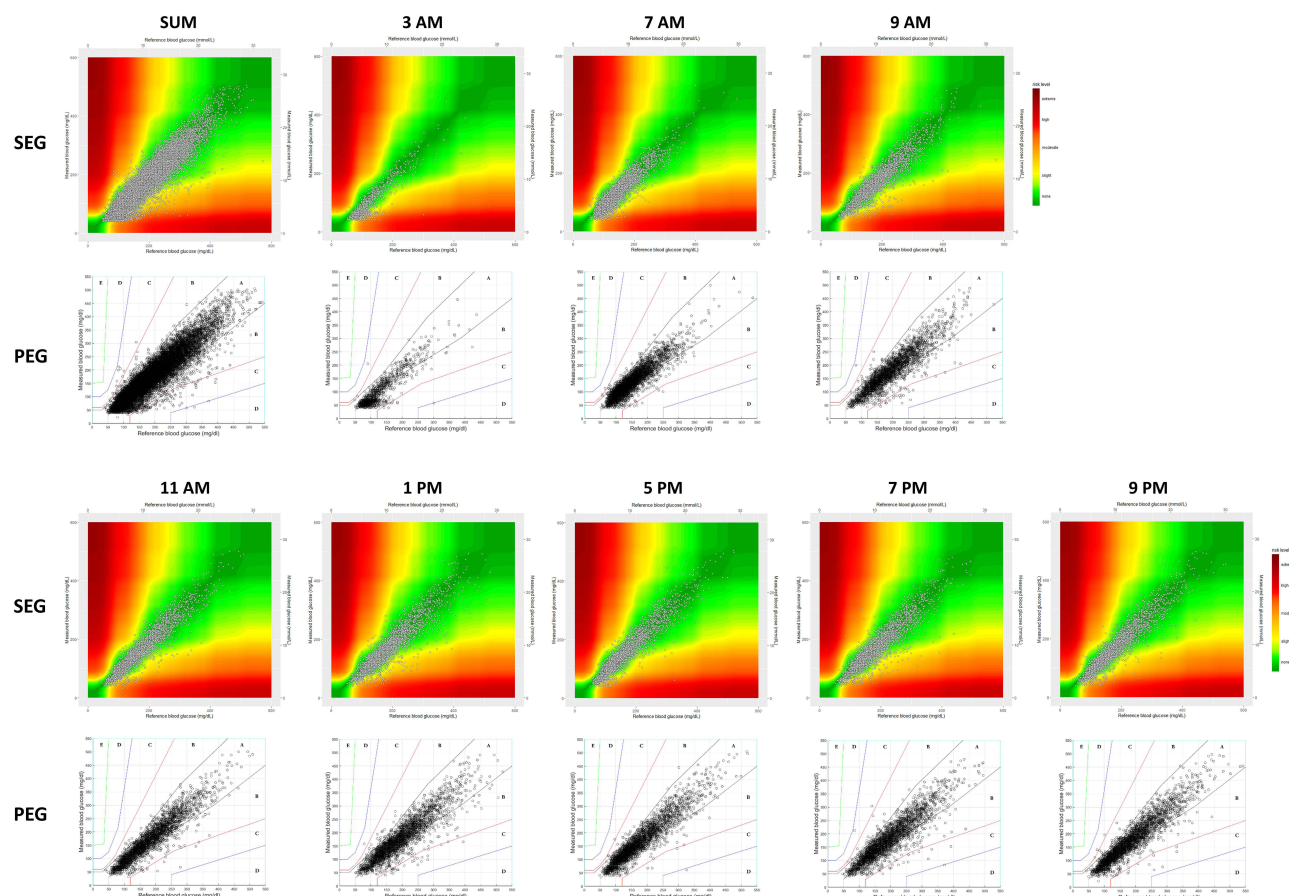


Figure 2 Comparison of the distribution of paired reading in risk zone in SEG and PEG.

hypoglycemia incidence, increased 24-h microalbuminuria and decreased eGFR, higher ratio of infection, increased incidences of DKA and hypertension, and higher incidence of cardiovascular and cerebrovascular events ($P<0.05$) (Table 2). The results of multivariate logistic regression analysis showed that hypoglycemia (OR 1.98 [95% CI 1.344–2.916], $P=0.001$), infection (OR 2.328 [95% CI 1.553–3.491], $P<0.001$), diabetic foot (OR 2.658 [95% CI 1.187–5.951], $P=0.017$), DKA (OR 2.602 [95% CI 1.005–6.735], $P=0.017$), and hypertension (Grade 2: OR 1.895 [95% CI 1.213–2.961], $P=0.005$; Grade 3: OR 1.609 [95% CI 1.099–2.355], $P=0.014$) were independent risk factors that affect FCGM accuracy in hospitalized patients (Table 3).

Discussion

Although the reliability and credibility of FCGM in glucose monitoring have been extensively discussed, its accuracy is still not fully documented in type 2 diabetes. Furthermore, methods using Clark Error Grid (CEG) and PEG have limited the accuracy in assessing FCGM precision and reliability, which has been reported to be less accurate in the hypoglycemic range.^{13,17–19} In the present study, 25,579 paired readings from 742 patients were evaluated. We found that FCGM mostly underestimated blood glucose levels, particularly at night with the least accuracy. SEG analysis revealed that diabetes complications and related comorbidities could impair FCGM accuracy.

In our study, the hypoglycemic state in T2D patients affected FCGM accuracy, especially nocturnal hypoglycemia. A study reported MARD of FCGM was generally 9.56–15.4%.¹¹ Bonora et al suggested that CGM accuracy at a MARD of 10–17% was clinically acceptable. In the present study, overall MARD was 14%.⁹ However, the MARD at 3 AM time point was extremely high, up to 24.5%, which could be a result of the higher frequency of hypoglycemia at 3 AM. Some studies have revealed poor FCGM accuracy at low blood glucose level. For example, Olafsdottir et al found that the MARD was 20.3% when the blood glucose level was <72 mg/dL,¹⁸ and Moser et al also reported that the MARD of

Table 2 Clinical Characteristics of Patients with SEG C/D Risk Zones

	Patients with C/D Risk Zone		Z/χ^2	P
	No (N=327)	Yes (N =415)		
Age (years)	61 (52, 70)	65 (56, 75)	-3.916	<0.001
Gender				
Male	176 (53.8)	197 (47.5)	-1.717	0.086
Female	151 (46.2)	218 (52.5)		
Duration (years)	6.00 (0.75, 10.00)	9.00 (2.00, 11.00)	-3.423	0.001
Ketone (mmol/L)	0.4 (0.2, 0.6)	0.4 (0.3, 0.7)	-1.384	0.166
BMI (kg/m²)	24.57 (22.27, 26.91)	23.98 (21.54, 27.07)	-1.176	0.240
HbA1c (%)	9.5 (7.6, 11.8)	8.1 (6.7, 10.9)	-4.947	<0.001
HgAb (g/L)	132 (121, 144)	122 (108, 136)	-6.664	<0.001
Creatinine (umol/L)	74 (60, 90)	80 (65, 110)	-3.541	<0.001
eGFR (mL/min)	89.89 (71.69, 108.24)	79.15 (55.19, 101.68)	-4.262	<0.001
Plasma colloid osmotic pressure (mOsm/kg)	284.59 (282.02, 288.00)	284.00 (280.22, 287.46)	-2.541	0.011
Total cholesterol (mmol/L)	4.55 (3.76, 5.39)	4.19 (3.42, 5.04)	-4.224	<0.001
TG (mmol/L)	1.55 (1.00, 2.28)	1.34 (0.95, 1.83)	-3.388	0.001
HDL cholesterol (mmol/L)	0.99 (0.83, 1.16)	1.00 (0.83, 1.22)	-0.867	0.386
LDL cholesterol (mmol/L)	2.86 (2.12, 3.61)	2.60 (1.92, 3.36)	-3.090	0.002
Albumin (g/L)	38 (36.2, 40.8)	37 (35, 40)	-3.107	0.002
24h microalbuminuria (mg/24h)	141.10 (92.00, 229.00)	172.80 (105.00, 364.45)	-3.209	0.001
Hypoglycemia events				
Yes	54 (16.5%)	124 (29.9%)	-4.230	<0.001
No	273 (83.5%)	291 (70.1%)		
Infection				
Yes	48 (14.7%)	132 (31.8%)	-5.400	<0.001
No	279 (85.3%)	283 (68.2%)		
DKA				
Yes	7 (2.1%)	20 (4.8%)	2.204	0.028
No	320 (97.9%)	395 (95.2%)		
Diabetic foot				
Yes	9 (2.8%)	36 (8.7%)	-3.454	0.001
No	318 (97.2%)	379 (91.3%)		
Cardiovascular and cerebrovascular events				
Yes	100 (30.6%)	177 (42.7%)	-3.372	0.001
No	225 (69.4%)	238 (57.3%)		
HBP				
Yes	143 (43.7%)	252 (60.7%)	-4.602	<0.001
No	184 (56.3%)	163 (39.3%)		
Insulin dose (U)	38 (7, 56)	24 (0, 45)	-5.163	<0.001

Note: Data are expressed as n (%) or median (quartile, 25th and 75th percentiles).

FCGM was even as high as 31.6% during hypoglycemia.¹⁷ Moreover, our results indicated that in patients who experienced hypoglycemia, the high-risk rate of FCGM/REF pairs was twice as high as in patients without hypoglycemia. It is partially because that hypoglycemia could affect the interstitial glucose concentration by affecting blood flow and vascular permeability.²⁰ And according to the ISO 15197:2013 standard, CGM should comply with the 95% accuracy criteria. However, overall FCGM accuracy was only 63.1% and decreased to 34% at 3 AM in our study. These findings demonstrated the importance of interpreting FCGM data and improving FCGM technology in the setting of hypoglycemia.

The error grid is a commonly used tool for evaluating FCGM accuracy per the ISO 15197:2013 standard criteria.²¹ When the CEG and PEG were developed (in the late 1980s and the early 1990s), SMBG was a relatively new instrument with a relatively low analytical accuracy, and CEG and PEG were effective in assessing its accuracy, although the

Table 3 Independent Factors Affect the Accuracy of FCGM

	B	SE	P	OR	95% CI for OR	
Hb	−0.014	0.004	0.001	0.986	0.977	0.994
Hypoglycemia events	0.683	0.198	0.001	1.98	1.344	2.916
Infection	0.845	0.207	<0.001	2.328	1.553	3.491
Diabetic foot	0.978	0.411	0.017	2.658	1.187	5.951
Insulin dose	−0.014	0.003	<0.001	0.986	0.98	0.992
DKA	0.956	0.485	0.049	2.602	1.005	6.735
Hypertension[†]						
Grade 1	−0.064	0.348	0.854	0.938	0.474	1.855
Grade 2	0.639	0.228	0.005	1.895	1.213	2.961
Grade 3	0.476	0.194	0.014	1.609	1.099	2.355

Note: [†]Define hypertension grade according to European Society of Cardiology/European Society of Hypertension guidelines.

methods for evaluating SMBG accuracy were not rigorous enough. With a significant improvement in SMBG performance in recent years, the CEG and PEG seem no longer applicable to properly assess the accuracy of new equipment.¹⁶ In CEG and PEG, every point within the same discrete risk zones has the same degree of risk. Compared to CEG and PEG, the SEG is a continuous and three-dimensional graph plotted on two dimensions that allow each point to have its risk value. The SEG appears more capable of assessing the clinical risk of device errors than the CEG and PEG.¹⁶ In the present study, although PEG showed a similar overall evaluation trend to SEG in the paired blood glucose assessment, the SEG represented detailed stratification and high sensitivity for the paired data with potential clinical risk. Chandnani et al also reported that high-risk levels were more frequent when analyzing paired readings with SEG than with PEG.²² Compared with PEG, our data revealed the SEG should be more conducive to properly evaluating FCGM performance and identifying potential adverse clinical decisions. For example, in [Supplementary Table 3](#), the No. 22 paired reading (FCGM 49 mg/dL vs REF 142 mg/dL) was displayed in SEG risk zone D, but in PEG risk zone B. The risk zone B in PEG is clinically acceptable; however, it should be an unacceptable risk because the clinical decision may lead to adverse consequences according to the FCGM value (49 mg/dL). In the No. 22 case, the condition would be mistaken for hypoglycemia and would increase to a higher level if the patient is given rapid sugar supplementation. Obviously, it completely deviates from the goal of blood glucose self-management. In addition, we found that almost all FCGM values in SEG risk zone D indicated hypoglycemia, whereas paired REF values indicated the absence of hypoglycemia. These results suggest that FCGM, while being highly sensitive in reporting hypoglycemia, is associated with low specificity and potentially high clinical risk.

Diabetes comorbidities and complications are common in T2D patients, but their impact on FCGM accuracy remains to be fully explored. It is known that more than 5% of diabetes patients experience foot ulcers, and the cumulative lifetime rate could be up to 15%,²³ which is the main reason for amputation in diabetes patients. DKA is also one of the most common conditions in patients with poorly managed diabetes.²⁴ Both DKA²⁵ and hypertension²⁶ could cause endothelial dysfunction through oxidative stress, which could affect microcirculation and glucose delivery to the interstitium.²⁷ Hypertension also increases the risk of progression of microvascular complications in diabetes patients, such as diabetic nephropathy and retinopathy.^{28,29} Undergoing hemodialysis in T2D patients with diabetic nephropathy could elevate MRAD and deteriorate the FCGM accuracy.³⁰ These studies suggest the necessity of exploring the effect of diabetes complications and related comorbidities on FCGM accuracy in patients in real-world settings. Reineke et al reported that DKA influenced CGMS accuracy (CGMS Gold, Medtronic MiniMed, Northridge, CA) using CEG and PEG analysis in 13 dogs and 11 cats.³¹ But the subjects were animals, not patients, which limited its interpretation in the clinical setting. In the present study, we found that infection, diabetic foot, DKA, and hypertension were independent risk factors for a high-risk value in patients using SEG analysis.

Conclusion

This study has both limitations and strengths. The study collected data from patients with T2D only and did not include patients with T1D, which would limit the generalizability of the results in diabetes. Moreover, the reference method was not sophisticated methods such as PCA-hexokinase method and the isotope dilution gas chromatography-mass spectrometry method, nor did the study include the additional blood glucose meter, to obtain a more desirable assessment of the FCGM performance. Nevertheless, our data delivers the valuable evaluation of the FCGM system in real-world settings. Our study indicates the lowest FCGM accuracy at 3 AM compared with other daily timepoints, and diabetes complications impair FCGM accuracy. Moreover, compared with PEG analysis, SEG could more accurately evaluate the FCGM performance. Overall, the present data highlights the importance of properly interpreting FCGM data in T2D patients, especially with diabetes complications or at nocturnal, to avoid improper intervention.

Data Sharing Statement

The data used to support the findings of this study may be released upon application to the Second Affiliated Hospital of Guangzhou Medical University, which can be contacted through Prof. Tao Du (email: dutao@gzhmu.edu.cn).

Disclosure of Ethical Statements

This study was approved by the academic ethics review boards of the hospital, the Second Affiliated Hospital of Guangzhou Medical University. Informed consents were obtained from all patients.

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Disclosure

The authors declare no conflicts of interest in this work.

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