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ORIGINAL RESEARCH

Correlation Between Blood Urea Nitrogen and Short- and Long-Term Glycemic Variability in Elderly Patients with Type 2 Diabetes Mellitus Who Were hospitalized:A Retrospective Study

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Objective: Type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by insulin resistance and progressively impaired insulin secretion resulting in dynamic fluctuations in glucose levels.High blood urea nitrogen (BUN) levels have been linked to decreased insulin sensitivity, suppressed insulin synthesis and increased risk of incident diabetes mellitus in humans as well as insulin use in patients with T2DM.This study characterize the association between BUN levels and short-term and long-term glycemic variability(GV) in the elderly patients with T2DM who were hospitalized.

Methods: A total of 927 elderly patients with T2DM were included in the study. The short-term GV was quantified using parameters such as standard deviation (SD), coefficient of variation (CV), time in range (TIR), and mean amplitude of glycemic excursions (MAGE), based on multi-point fingertip blood glucose monitoring. The long-term GV was quantified using parameters such as SD, CV, variation independent of the mean (VIM), and average successive variability (ARV), based on fasting blood glucose(FPG). The relationship between BUN levels and short-term and long-term GV in elderly T2DM who were hospitalized was explored using methods such as Spearman correlation coefficient, linear regression analysis, logistic regression analysis, and interaction tests.

Results: In elderly patients with T2DM were hospitalized, there is a significant correlation between BUN levels and both short-term and long-term GV. BUN is negatively correlated with the GV parameter TIR (r=−0.12, *P*=0.000), and positively correlated with SD (r=0.12, *P*=0.000), CV (r=0.07, *P*=0.026), MAGE (r=0.11, *P*=0.001), FPG-SD (r=0.08, *P*=0.013), and FPG-CV (r=0.08, *P*=0.014). Furthermore, the association remains consistent across different age, gender, BMI, and haemoglobin A1c (HbA1c) subgroups (*P* interaction > 0.05).

Conclusion: In elderly patients with T2DM were hospitalized, BUN levels were positively associated with GV.Therefore, monitoring BUN levels were beneficial in assessing the degree of GV.

Keywords: diabetes mellitus, glycemic variability, vascular lesions of diabetes mellitus, glycemic variability parameters

Introduction

Glycemic variability (GV), also known as blood glucose fluctuations, refer to the dynamic changes in blood glucose levels between high and low values. It encompasses two main categories: long-term GV, which refers to the variations in blood glucose levels over a period of weeks to months, or even years, during long-term follow-up, including the fluctuations in haemoglobin A1c (HbA1c), fasting plasma glucose(FPG), or postprandial blood glucose;[1] and short-term GV, which represents the variations in blood glucose levels within a day or between different times of the day.

Clinical physicians often use GV parameters such as standard deviation (SD), coefficient of variation (CV), time in range (TIR), mean amplitude of glycemic excursions (MAGE), variation independent of the mean (VIM), and average successive variability (ARV) to quantify short-term and long-term GV. Among these, SD, CV, TIR, and MAGE are

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generally used to quantify short-term GV, while FPG standard deviation (FPG-SD), FPG coefficient variation (FPG-CV), FPG variation independent of the mean (FPG-VIM) and FPG average successive variability (FPG-ARV) are primarily used to quantify long-term GV.

Variations in blood glucose levels may increase risk of incident diabetes-related consequences such as kidney disease, retinopathy, heart and neurological complications. The activation of platelets, oxidative stress pathways, endothelial cell dysfunction, and chronic inflammation are thought to be the root causes of these problems.[2–4] The development and occurrence of microalbuminuria, diabetic nephropathy(DN),[5] diabetic retinopathy(DR), and cardiovascular autonomic neuropathy(CAN) can all be slowed down by maintaining TIR.[6] Furthermore, TIR is significantly negatively correlated with cardiovascular disease and increased risk of all-cause mortality.[7] Long-term GV parameters such as FPG-SD, FPG-CV, HbA1c-SD, and HbA1c-CV at a follow-up of 24 months are risk predictors for all microvascular and macrovascular complications, and their predictive power is better than average HbA1c.[8] Therefore, it can be seen that both short-term and long-term GV are associated with diabetic microvascular and macrovascular diseases.

The potential mechanism underlying the dysregulation of GV lies in insulin resistance.The kidneys play a crucial role in maintaining blood glucose homeostasis, and BUN is considered a common and important indicator for assessing renal function in the body. Research has shown that BUN represents the nitrogen content in urea molecules, which are different units of the same substance. Urea is a major metabolic product of proteins, freely filtered by the glomeruli in the kidneys but not secreted, and subsequently reabsorbed by the renal tubules.[9] Possible contributors of the dynamic disturbance of blood glucose include acidosis of the metabolic system, age, insulin resistance, uremic toxin accumulation, particularly BUN, oxidative stress, and chronic inflammation.[10–12] Patients with chronic kidney disease (CKD) often experience dynamic disruptions in blood glucose and insulin levels, CKD reduces insulin sensitivity, which further leads to impaired pancreatic β-cell function and insulin secretion in the later stages.[12] Additionally, there is a correlation between CKD and decreased insulin clearance, especially in patients with moderate to severe CKD.[13] It is worth noting that research suggests that the insulin secretion defect in CKD is mainly caused by elevated circulating urea levels, especially in the later stages of CKD.[14] Multiple experimental evidence suggests that elevated levels of urea may lead to decreased insulin sensitivity and insulin secretion through oxidative stress, chronic inflammation, and post-translational modifications induced.[9,15,16] Therefore, it can also be considered that high levels of BUN contribute to insulin resistance and insulin secretion defects through the mechanisms mentioned above.There is existing experimental evidence that shows an increase in BUN levels can increase the risk of developing diabetes in non-diabetic individuals[17,18] as well as the risk of insulin usage in patients with T2DM. In other words, as blood BUN levels rise, it may become more difficult to control blood glucose levels in patients with T2DM, which means that high BUN levels may contribute to blood glucose fluctuations.[19]

In light of this, we assume that when the BUN increases, insulin sensitivity declines, insulin secretion deficiencies become more obvious, and GV may also accelerate in patients with T2DM. The relationship between BUN levels and GV in patients with T2DM has not yet been examined though. The relationship between BUN levels and GV in the elderly patients with T2DM were hospitalized is further examined in this study.

Materials and Methods

Study Population

927 elderly patients with type 2 diabetes were selected from various departments of Gusu School, Nanjing Medical University, The First People's Hospital of Kunshan who underwent inpatient treatment and received regular physical examinations at several community hospitals (Lujia, Zhenchuan, Penglang, Bailu, Qingyang, and Jiangpu) in collaboration with Kunshan First People's Hospital from January 17, 2014 to September 27, 2022. Inclusion criteria were as follows: (1) meeting the diagnostic and classification criteria for type 2 diabetes published by the World Health Organization (WHO) in 1999;[20] (2) Patients who had blood glucose monitoring at least three intervals during the day were the main subjects in this study (in other words, blood glucose monitoring at least 3 times per day); (3) During the follow-up of community physical examinations follow-ups, we conducted an annual assessment of FPG (The duration of FPG measurement is 1 year; in other word, Measure FPG once per-year) for each patient. Ultimately, the subjects in this study had overall annually FPG measures at community hospitals during the follow-up period that were equivalent to or

greater than three times; (4) Age sixty years or older.Exclusion criteria: (1) Other types of diabetes, such as type 1 diabetes, gestational diabetes, and special types of diabetes; (2) During the follow-up period of community physical examinations follow-ups, monitoring of annual FPG (The duration of FPG measurement is 1 year), and the overall annually FPG measurements conducted at any community hospital for the subjects is less than three times; (3) Less than three intervals daily blood glucose monitoring during hospitalization; (4) Long-term use of medications such as corticosteroids and antipsychotic drugs that may affect blood glucose levels; (5) Presence of acute infection, severe liver or kidney dysfunction, or hypoalbuminemia; (6) Coexistence of other endocrine disorders, such as hyperthyroidism. The Ethics Committee of The First People's Hospital of Kunshan (Ethics Review Approval: IEC-SOP-007-A07-V4.0) has approved this research study, and all subjects were informed and consented prior to treatment.The research process complies with the Helsinki Declaration.

Study Methods

Baseline Data Collection

(1) General information: name, ID number, age, gender, past medical history, Height (H), Body weight (BW), Waist circumference (WC), Systolic blood pressure (SBP), Diastolic Blood pressure (DBP), and calculation of body mass index (BMI) based on corresponding basic body parameters.(2) Biochemical tests were conducted by professional personnel on the fasting venous blood samples of the research subjects. Specialized automated biochemical analyzers and analysis reagents were used for the measurements. The tested indicators included: Fasting Plasma Glucose (FPG), HbA1c, Albumin, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Blood Urea Nitrogen (BUN), Serum Creatinine (Scr), Soluble Uric Acid (SUA), Total Cholesterol (TC), Triglycerides (TG), Low-Density Lipoprotein Cholesterol (LDL-C), High-Density Lipoprotein Cholesterol (HDL-C). The estimated Glomerular Filtration Rate (eGFR) was calculated using the modified MDRD formula for Chinese individuals. BUN was measured at the beginning of the measurement of GV, and the other indicators were measured at the same time point of BUN. In a other word, all the biochemical indicators mentioned were measured before of the measurement of GV.The sensitive information such as the ID numbers and names of all enrolled patients were de-identified and cleansed. The patients were then assigned new identifiers and linked to their corresponding baseline data, basic body measurements, and biochemical indicators.

Assessment of GV

Healthcare professionals use a method called self-monitoring of blood glucose (SMBG) to collect blood glucose levels from the capillaries of the fingertips. Typically, blood glucose measurements are taken in the morning before breakfast, 2 hours after breakfast, before lunch, 2 hours after lunch, before dinner, 2 hours after dinner, and before bedtime.

Various parameters such as SD, CV, TIR, and MAGE are used to assess short-term GV. SD represents the square root of the mean squared deviation (reference value <2.0 mmol/L).[21] CV is calculated as (SD/mean) x 100% and reflects the magnitude of blood glucose changes. The target CV for the Chinese population is ≤33%.[20] TIR is calculated by dividing the number of blood glucose measurements during hospitalization that fall within the range of 3.9–10.0 mmol/L by the total number of blood glucose measurements, and then multiplying by 100%. TIR > 70% is generally considered the target for glucose control, with higher TIR indicating better control of glucose fluctuations.[22] MAGE represents the extent of glucose fluctuations throughout the day, excluding fluctuations that do not exceed a certain threshold (usually 1SD), and calculating the average magnitude of glucose fluctuations based on the first significant change in direction.[23] The normal reference value for MAGE is < 3.9 mmol/L.[21] In this study, we classified the patients into well-controlled and poorly-controlled categories based on these measures of GV, and conducted logistic regression analysis.

The long-term GV parameters analyzed in this study are based on FPG collected from multiple community hospitals. These parameters, including SD, CV, VIM, and ARV, are used to represent the degree of variation. For example, FPG-SD refers to the arithmetic square root of the squared deviation of FPG from the mean, while FPG-CV is calculated as (FPG-SD/FPG-mean) × 100%. VIM is determined by dividing SD by the exponent β of the logarithmic curve fitting, where β is the standardized coefficient of the power function fitting of SD to the mean.[24] ARV represents the average difference between consecutive values and provides a rough estimate of each fluctuation, rather than simply measuring the dispersion of the data.[25] VIM further eliminates the correlation with the mean when compared to CV.

Statistical Analysis

We conducted statistical analysis on the data using SPSS 25.0 software. The Kolmogorov–Smirnov (K-S) test was used to assess the normality of continuous variable data distribution characteristics, assess the distribution characteristics of continuous variables. Continuous variables that follow a normal distribution were described using the mean ± standard deviation, while non-normal distribution variables were described using the median and quartiles. Categorical variables were described using numbers and percentages. For comparing normally distributed continuous variables between two groups, an independent samples *t*-test was used. We compare continuous variables with a normal distribution between three groups using analysis of variance (ANOVA).For comparing non-normally distributed continuous variables, a non-parametric Mann–Whitney *U*-test was used.Using Spearman correlation, linear regression analysis, logistic regression analysis, and interaction tests, we investigated the correlation between BUN levels and short-term and long-term GV in elderly patients with T2DM. We performed a two-sided test with a significance level of α=0.05, and considered a *P*-value less than 0.05 to indicate statistical significance of the results.

Results

Baseline Characteristics of the Overall Population and Different Gender Subgroups

Among the 927 participants, males had higher waist circumference (WC), alanine aminotransferase (ALT), serum uric acid (SUA), and serum creatinine (Scr) levels compared to females ($P<0.05$). Conversely, males had lower body mass index (BMI), systolic blood pressure (SBP), albumin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels compared to females ($P<0.05$). However, there were no significant differences between the two groups in terms of age, diastolic blood pressure (DBP), glycated hemoglobin (HbA1c), blood urea nitrogen (BUN), estimated glomerular filtration rate (eGFR), and aspartate aminotransferase (AST) ($P>0.05$). Importantly, among the different gender subgroups, male patients had a relatively lower long-term glucose variability parameter, FPG-VIM ($P<0.05$), while there were no significant differences between males and females in terms of other long-term glucose variability parameters such as FPG-SD, FPG-CV, FPG-ARV, and short-term glucose variability parameters such as TIR, SD, CV, and MAGE ($P>0.05$), as shown in Table 1.

Table 1 Baseline Characteristics of the Overall Population and Different Gender Subgroups

	Total	Female (N=496)	Male (N=431)	*P*-value
Age (years)	72.95 ± 6.49	72.73 ± 6.35	73.19 ± 6.66	0.286
WC (cm)	86.54 ± 7.38	86.06 ± 7.44	87.11 ± 7.28	0.031*
BMI (kg/m^2)	25.15 ± 3.00	25.44 ± 3.08	24.82 ± 2.87	0.002**
DBP (mmHg)	79.23 ± 7.53	78.84 ± 7.31	79.68 ± 7.76	0.089
SBP (mmHg)	141.90 ± 13.77	143.18 ± 13.38	140.42 ± 14.08	0.002**
Albumin (g/L)	39.16 ± 4.51	39.53 ± 4.20	38.74 ± 4.81	0.009**
HbA1c (%)	8.11 ± 1.91	8.10 ± 1.78	8.13 ± 2.08	0.825
TC (mmol/L)	4.09 ± 1.05	4.25 ± 1.08	3.91 ± 0.98	<0.001**
HDL-C (mmol/L)	1.26 ± 0.30	1.31 ± 0.32	1.21 ± 0.26	<0.001**
LDL-C (mmol/L)	2.47 ± 0.85	2.56 ± 0.86	2.37 ± 0.83	0.001**
TG (mmol/L)	1.20 (0.86–1.73)	1.29 (0.96–1.87)	1.11 (0.76–1.55)	<0.001**
ALT (U/L)	19.00 (14.00–27.00)	18.00 (13.00–26.00)	20.00 (15.00–28.00)	0.024 *
AST (U/L)	21.00 (16.00–28.00)	21.00 (16.00–27.75)	21.00 (16.50–28.00)	0.254
BUN (mmol/L)	6.50 (5.20–7.94)	6.33 (5.10–7.79)	6.61 (5.22–8.20)	0.290
SUA (mmol/L)	316.51 ± 105.92	302.10 ± 105.33	332.83 ± 104.33	<0.001**
Scr (mmol/L)	64.00 (51.00–85.00)	56.00 (49.00–74.00)	74.00 (61.00–96.00)	0.011**
eGFR (mL/min/1.73m^2)	97.03 (70.41–116.04)	98.20 (70.50–115.27)	95.48 (70.21–118.66)	0.653

(*Continued*)

Table 1 (Continued).

	Total	Female (N=496)	Male (N=431)	*P*-value
Parameters of the Short-term Glycemic Variability				
MEAN (mmol/L)	10.02 ± 2.05	10.12 ± 1.98	9.90 ± 2.12	0.091
TIR (%)	0.58 ± 0.23	0.57 ± 0.22	0.59 ± 0.24	0.136
SD (mmol/L)	3.19 ± 1.24	3.21 ± 1.21	3.17 ± 1.27	0.640
CV (%)	0.31 ± 0.09	0.31 ± 0.09	0.31 ± 0.10	0.697
MAGE (mmol/L)	5.62 ± 2.08	5.60 ± 2.00	5.65 ± 2.17	0.718
Parameters of Long-term Glycemic Variability				
FPG-MEAN (mmol/L)	7.58 ± 1.78	7.69 ± 1.75	7.45 ± 1.81	0.043*
FPG-SD (mmol/L)	1.40 ± 0.95	1.38 ± 0.86	1.42 ± 1.05	0.573
FPG-CV (%)	0.17 ± 0.10	0.17 ± 0.09	0.18 ± 0.11	0.320
FPG-ARV (mmol/L)	16.40 (10.36–25.38)	16.30 (10.75–25.18)	16.75 (10.02–25.62)	0.568
FPG-VIM (mmol/L)	7.58 ± 1.78	7.69 ± 1.75	7.45 ± 1.81	0.043*

Notes: *P<0.05 **P<0.01. Age (years). For continuous variables that follow a normal distribution, we can describe them using the mean plus or minus the standard deviation. However, for continuous variables that do not follow a normal distribution, we can describe them using the median and quartiles. As for count data, we can simply report the number (N) and the percentage (%) it represents.

Abbreviations: WC, waist circumference; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; Albumin, HbA1c, glycated hemoglobin; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; SUA, serum uric acid; Scr, serum creatinine; eGFR, estimated glomerular filtration rate; MEAN, mean glycemic variability; TIR, time in range; SD, standard deviation; CV, coefficient of variation; MAGE, mean amplitude of glucose excursions; FPG-MEAN, mean fasting plasma glucose; FPG-SD, fasting plasma glucose standard deviation; FPG-CV, fasting plasma glucose coefficient of variation; FPG-ARV, average real variability of fasting plasma glucose; FPG-VIM, fasting plasma glucose variability independent of the mean.

Baseline Characteristics of the Overall Cohort According to BUN Tertiles at Baseline

Characteristics of the included participates at baseline are shown in Table 2.We can observe that as BUN levels increase in the three groups of BUN T1-3 study populations, the average age, SBP, BUN, SUA, and Scr all show a gradual increase (P<0.05). Conversely, the eGFR shows a gradual decrease with increasing BUN levels (P<0.05). Additionally, there are differences in albumin levels among the three groups. Of particular note, among the BUN T1-3 study

Table 2 Baseline Characteristics of the Overall Cohort According to BUN Tertiles at Baseline

	T1 (N=308)	T2 (N=310)	T3 (N=309)	*P*-value
Age (years)	71.65 ± 6.09	72.72 ± 6.26	74.47 ± 6.81	<0.001**
Gender (Female)	175 (56.82%)	166 (53.55%)	155 (50.16%)	0.253
Gender (Male)	133 (43.18%)	144 (46.45%)	154 (49.84%)	0.253
WC (cm)	86.91 ± 7.29	86.71 ± 7.11	86.01 ± 7.72	0.284
BMI (kg/m^2)	25.23 ± 3.02	25.28 ± 2.94	24.94 ± 3.03	0.320
DBP (mmHg)	79.36 ± 7.38	79.17 ± 7.49	79.16 ± 7.74	0.935
SBP (mmHg)	140.42 ± 13.72	140.92 ± 13.66	144.35 ± 13.65	<0.001**
Albumin (g/L)	39.46 ± 4.46	39.97 ± 3.85	38.13 ± 4.91	<0.001**
HbA1c (%)	8.04 ± 1.76	7.98 ± 1.86	8.34 ± 2.10	0.102
TC (mmol/L)	4.08 ± 0.98	4.08 ± 0.95	4.11 ± 1.21	0.935
HDL-C (mmol/L)	1.27 ± 0.29	1.26 ± 0.29	1.25 ± 0.31	0.719
LDL-C (mmol/L)	2.48 ± 0.81	2.45 ± 0.76	2.48 ± 0.97	0.909
TG (mmol/L)	1.15 (0.85–1.63)	1.23 (0.90–1.75)	1.23 (0.83–1.83)	0.157
ALT (U/L)	19.00 (13.00–28.00)	20.00 (15.00–27.00)	18.00 (14.00–26.00)	0.924
AST (U/L)	20.00 (16.00–28.00)	21.00 (17.00–27.00)	22.00 (16.00–29.00)	0.688
BUN (mmol/L)	4.70 (4.12–5.19)	6.50 (6.10–7.08)	8.78 (7.95–10.80)	<0.001**
SUA (mmol/L)	275.34 ± 84.05	311.26 ± 91.55	362.17 ± 118.81	<0.001**
Scr (mmol/L)	55.00 (48.00–68.00)	64.00 (52.00–83.00)	78.00 (61.00–115.00)	<0.001**
eGFR (mL/min/1.73m^2)	110.89 (93.47–131.79)	95.32 (76.83–112.96)	76.56 (53.52–103.44)	<0.001**

(*Continued*)

Table 2 (Continued).

	T1 (N=308)	T2 (N=310)	T3 (N=309)	*P*-value
Parameters of the Short-term Glycemic Variability				
MEAN (mmol/L)	9.79 ± 1.86	9.95 ± 2.11	10.31 ± 2.13	0.006**
TIR (%)	0.60 ± 0.22	0.58 ± 0.22	0.55 ± 0.24	0.019*
SD (mmol/L)	3.05 ± 1.08	3.20 ± 1.31	3.33 ± 1.30	0.014*
CV (%)	0.31 ± 0.08	0.32 ± 0.10	0.32 ± 0.09	0.322
MAGE (mmol/L)	5.41 ± 1.81	5.60 ± 2.16	5.85 ± 2.23	0.035*
Parameters of Long-term Glycemic Variability				
FPG-MEAN (mmol/L)	7.57 ± 1.71	7.43 ± 1.76	7.73 ± 1.87	0.117
FPG-SD (mmol/L)	1.36 ± 0.88	1.31 ± 0.97	1.53 ± 1.00	0.014*
FPG-CV (%)	0.17 ± 0.09	0.17 ± 0.10	0.19 ± 0.10	0.029*
FPG-ARV (mmol/L)	16.64 (10.41–24.65)	15.61 (9.49–23.90)	17.89 (11.19–27.83)	0.041*
FPG-VIM (mmol/L)	7.57 ± 1.71	7.43 ± 1.76	7.73 ± 1.87	0.117

Notes: *P<0.05 **P<0.01.

populations, short-term GV parameters show a decrease in TIR with increasing BUN levels, while parameters such as MAGE and SD show an upward trend (P<0.05). Furthermore, there are differences in FPG-SD, FPG-CV, and FPG-ARV among the three groups as BUN levels increase (P<0.05).However, there were no statistically significant differences (P>0.05) in gender, WC, BMI, DBP, HbA1c, TC, TG, HDL-C, LDL-C, ALT, AST, as well as short-term GV parameter CV, and long-term GV parameter FPG-VIM difference among the three study populations.

The Relationship Between BUN and Short- and Long-Term GV in Elderly Patients with T2DM

In the elderly patients with T2DM, there is a negative correlation between BUN and the short-term GV parameter TIR (r=−0.12, P<0.01). BUN is positively correlated with SD (r=0.12, P<0.01), CV (r=0.07, P<0.05), MAGE (r=0.11, P<0.01), FPG-SD (r=0.08, P<0.05), and FPG-CV (r=0.08, P<0.05), all of which are GV parameters. Furthermore, these correlations remain significant even after adjusting for age and gender. However, no correlation was observed between BUN and CV, FPG-ARV, and FPG-VIM, as shown in Table 3.

Table 3 The Relationship Between BUN and Short- and Long-Term GV in Elderly Patients with T2DM

	r	r'
Parameters of the Short-term Glycemic Variability		
TIR	−0.12**	−0.13**
SD	0.12**	0.12**
CV	0.07*	0.06*
MAGE	0.11**	0.12**
Parameters of Long-term Glycemic Variability		
FPG-SD	0.08*	0.12**
FPG-CV	0.08*	0.11**
FPG-ARV	0.06	0.08*
FPG-VIM	0.03	0.07*

Notes: *P<0.05, **P<0.01, r: correlation coefficient; r': Revised correlation coefficient after adjusting for age and gender.

Abbreviations: TIR, time in range; SD, standard deviation, CV, coefficient of variation; MAGE, mean amplitude of glucose excursions; FPG-MEAN, mean fasting plasma glucose; FPG-SD, fasting plasma glucose standard deviation; FPG-CV, fasting plasma glucose coefficient of variation; FPG-ARV, average real variability of fasting plasma glucose; FPG-VIM, fasting plasma glucose variability independent of the mean.

The Relationship Between BUN and Both Short- and Long-Term GV (Continuous Variables) Was Examined Using Linear Regression

The results show that after adjusting for age, gender, albumin, BMI, WC, DBP, SBP, TC, TG, HDL-C, LDL-C, ALT, AST, eGFR, Scr, SUA, etc. BUN is significantly associated with TIR (β=−0.01, 95% CI −0.02, −0.00, P<0.05), meaning that for every 1mmol/L increase in BUN, TIR decreases by 0.01%; BUN is significantly associated with SD (β=0.06, 95% CI 0.02, 0.10, P<0.01), meaning that for every 1mmol/L increase in BUN, SD increases by 0.06mmol/L; BUN is significantly associated with MAGE (β=0.10, 95% CI 0.04, 0.16, P<0.01), meaning that for every 1mmol/L increase in BUN, MAGE increases by 0.10mmol/L; BUN is significantly associated with CV (β=0.00, 95% CI 0.00, 0.01, P<0.05). BUN is also significantly associated with FPG-SD (β=0.05, 95% CI 0.03, 0.08, P<0.01), meaning that for every 1mmol/L increase in BUN, FPG-SD increases by 0.05mmol/L; BUN is significantly associated with FPG-ARV (β=0.63, 95% CI 0.16, 1.11, P<0.01), meaning that for every 1mmol/L increase in BUN, FPG-ARV increases by 0.63mmol/L; BUN is significantly associated with FPG-VIM (β=0.10, 95% CI 0.05, 0.15, P<0.05), meaning that for every 1mmol/L increase in BUN, FPG-VIM increases by 0.10mmol/L; BUN is significantly associated with FPG-CV (β=0.00, 95% CI 0.00, 0.01, P<0.01), as shown in Table 4.

The Correlation Between BUN and Both Short- and Long-Term GV (Dichotomous Variables) Was Examined Using Logistic Regression Analysis

Previous studies have used CV>33%; TIR>70%; SD≥2.0mmol/L; MAGE≥3.9 as critical thresholds to categorize various short-term GV parameters into dichotomous variables of good and poor glycemic control.The following criteria were used to classify long-term GV measures as dichotomous variables for good and poor blood glucose control: FPG-SD quartiles, FPG-CV quartiles, FPG-ARV quartiles, and FPG-VIM quartiles. Performing logistic regression analysis on BUN and multiple dichotomous variables above it. Age, gender, albumin, BMI, WC, DBP, SBP, TC, TG, HDL-C, LDL-C, ALT, AST, eGFR, Scr, and SUA have all been taken into account. The findings were summarized in Table 5 and showed that BUN was still correlated with MAGE (OR=0.88, 95% CI 0.80, 0.97, P<0.01), the long-term blood glucose variability parameters FPG-SD (OR=1.06, 95% CI 1.02, 1.11, P<0.01), and FPG-CV (OR=1.05, 95% CI 1.01, 1.09, P<0.05), as well as a trend of correlation with TIR (OR=0.93, 95% CI 0.87, 1.00, P=0.054) and SD (OR=0.91, 95% CI 0.83, 1.00, P=0.060).

The Relationship Between BUN Levels and Short- and Long-Term GV Based on the Analysis of Subgroups by Gender, Age, HbA1c, and BMI

Further subgroup analysis was conducted to investigate the relationship between BUN and short- and long-term GV characteristics based on the findings of the linear regression analysis. With 75 years old as the cutoff, the volunteers were

Table 4 The Relationship Between BUN and Both Short- and Long-Term GV (Continuous Variables) Was Examined Using Linear Regression

	Non-Adjusted		Adjust I		Adjust II	
	β (95% CI)	*P*-value	β (95% CI)	*P*-value	β (95% CI)	*P*-value
Parameters of the Short-term Glycemic Variability						
TIR	−0.01 (−0.01, −0.00)	<0.001**	−0.01 (−0.01, −0.00)	<0.001**	−0.01 (−0.02, −0.00)	0.011*
SD	0.04 (0.02, 0.07)	0.001**	0.05 (0.02, 0.07)	<0.001**	0.06 (0.02, 0.10)	0.002**
CV	0.00 (−0.00, 0.00)	0.150	0.00 (0.00, 0.00)	0.050	0.00 (0.00, 0.01)	0.012*
MAGE	0.07 (0.03, 0.11)	0.001**	0.08 (0.04, 0.12)	<0.001**	0.10 (0.04, 0.16)	0.002**
Parameters of Long-term Glycemic Variability						
FPG-SD	0.03 (0.01, 0.05)	0.004**	0.03 (0.01, 0.05)	0.004**	0.05 (0.03, 0.08)	<0.001**
FPG-CV	0.00 (0.00, 0.00)	0.003**	0.00 (0.00, 0.00)	0.003**	0.00 (0.00, 0.01)	0.006**
FPG-ARV	0.32 (0.02, 0.63)	0.038*	0.32 (0.02, 0.63)	0.038*	0.63 (0.16, 1.11)	0.010*
FPG-VIM	0.02 (−0.02, 0.05)	0.289	0.02 (−0.02, 0.05)	0.289	0.10 (0.05, 0.15)	<0.001**

Notes: *P<0.05 **P<0.01; Age and gender were controlled for in Adjustment I, Adjustment II: adjusting for age, gender, albumin, BMI, WC, DBP, SBP, TC, TG, HDL-C, LDL-C, ALT, AST, eGFR, Scr, SUA.

Table 5 The Correlation Between BUN and Both Short- and Long-Term GV (Dichotomous Variables) Was Examined Using Logistic Regression Analysis

	Non-Adjusted		Adjust I		Adjust II	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**	**OR (95% CI)**	***P*-value**
Parameters of the Short-term Glycemic Variability						
TIR (≤70%;>70%)	0.94(0.89, 0.99)	0.012*	0.93(0.89, 0.98)	0.008**	0.93(0.87, 1.00)	0.054
SD (<2.0; ≥2.0)	0.95(0.90, 1.02)	0.136	0.93(0.87, 1.00)	0.046*	0.91(0.83, 1.00)	0.060
CV (≤33%;>33%)	1.02(0.98, 1.07)	0.289	1.04(0.99, 1.09)	0.119	1.05(0.98, 1.13)	0.131
MAGE (<3.9; ≥3.9)	0.93(0.87, 0.99)	0.028*	0.91(0.85, 0.98)	0.007**	0.88(0.80, 0.97)	0.009**
Parameters of Long-term Glycemic Variability						
FPG-SD二分位数	1.06(1.02, 1.11)	0.006**	1.06(1.02, 1.11)	0.006**	1.06(1.02, 1.11)	0.006**
FPG-CV二分位数	1.05(1.01, 1.09)	0.024*	1.05(1.01, 1.09)	0.024*	1.05(1.01, 1.09)	0.024*
FPG-ARV二分位数	1.03(0.99, 1.07)	0.133	1.03(0.99, 1.07)	0.133	1.03(0.99, 1.07)	0.133
FPG-VIM二分位数	1.00(0.96, 1.04)	0.993	1.00(0.96, 1.04)	0.993	1.00(0.96, 1.04)	0.993

Notes: *P<0.05 **P<0.01; Age and gender were controlled for in Adjustment I, Adjustment II: adjusting for age, gender, albumin, BMI, WC, DBP, SBP, TC, TG, HDL-C, LDL-C, ALT, AST, eGFR, Scr, SUA.

split into two groups depending on their ages. Additionally, they were separated into groups of men and women. For subgroup sensitivity analysis, the subjects were further separated into two subgroups based on a baseline HbA1c level of <8.5% and ≥8.5%.[26] The cutoff points for overweight and obesity were established at 24.0kg/m^2 and 28.0kg/m^2, respectively, according to the Chinese Obesity Working Group's (WGOC) recommended optimal cutoff points for body mass index (BMI) in Chinese people. As a result, BMI was divided into three categories: BMI<24kg/m^2, 24≤BMI<28kg/m^2, BMI>28kg/m^2.[27]

The interaction test was conducted using age, gender, BMI, and HbA1c as effect modifiers after accounting for covariates such as age, gender, albumin, BMI, WC, DBP, SBP, TC, TG, HDL-C, LDL-C, ALT, AST, eGFR, Scr, SUA, and others. The findings revealed a consistent correlation between BUN levels and short- and long-term GV across different subgroups (P interaction > 0.05), as shown in Tables 6 and 7. There is no subgroup effect on the correlation between BUN and GV in subgroup analysis.

Table 6 Subgroup Analysis of the Correlation Between BUN Levels and Short-termGV

	Subgroup	**β (95% CI)**	***P*-value**	***P* Interaction**
TIR	Age			0.665
	≥75	−0.01 (−0.02, −0.00)	0.038	
	<75	−0.01 (−0.02, −0.00)	0.024	
	Gender			0.284
	Female	−0.01 (−0.01, 0.00)	0.106	
	Male	−0.01 (−0.02, −0.00)	0.007	
	BMI			0.614
	<24	−0.01 (−0.02, −0.00)	0.023	
	≥24, <28	−0.01 (−0.02, 0.00)	0.066	
	≥28	−0.01 (−0.02, 0.00)	0.055	
	HbA1c			0.428
	<8.5	−0.003 (−0.011, 0.004)	0.392	
	≥8.5	0.001 (−0.010, 0.012)	0.853	

(*Continued*)

Table 6 (Continued).

	Subgroup	β (95% CI)	*P*-value	*P* Interaction
SD	Age			0.172
	≥75	0.05 (0.00, 0.09)	0.036	
	<75	0.08 (0.03, 0.13)	0.001	
	Gender			0.554
	Female	0.05 (0.01, 0.10)	0.020	
	Male	0.07 (0.02, 0.11)	0.004	
	BMI			0.930
	<24	0.06 (0.00, 0.12)	0.042	
	≥24, <28	0.06 (0.01, 0.10)	0.012	
	≥28	0.07 (0.01, 0.12)	0.025	
	HbA1c			0.657
	<8.5	0.023 (−0.017, 0.063)	0.255	
	≥8.5	0.010 (−0.045, 0.066)	0.715	
CV	Age			0.111
	≥75	0.00 (−0.00, 0.01)	0.143	
	<75	0.01 (0.00, 0.01)	0.003	
	Gender			0.712
	Female	0.00 (−0.00, 0.01)	0.051	
	Male	0.00 (0.00, 0.01)	0.024	
	BMI			0.857
	<24	0.00 (−0.00, 0.01)	0.236	
	≥24, <28	0.00 (0.00, 0.01)	0.021	
	≥28	0.00 (−0.00, 0.01)	0.079	
	HbA1c			0.111
	<8.5	0.00 (−0.00, 0.01)	0.143	
	≥8.5	0.01 (0.00, 0.01)	0.003	
MAGE	Age			0.220
	≥75	0.08 (0.01, 0.15)	0.031	
	<75	0.13 (0.05, 0.21)	0.002	
	Gender			0.584
	Female	0.09 (0.01, 0.16)	0.019	
	Male	0.11 (0.03, 0.19)	0.005	
	BMI			0.963
	<24	0.11 (0.01, 0.21)	0.031	
	≥24, <28	0.10 (0.02, 0.17)	0.010	
	≥28	0.10 (0.00, 0.20)	0.045	
	HbA1c			0.971
	<8.5	0.030 (−0.040, 0.099)	0.400	
	≥8.5	0.032 (−0.066, 0.129)	0.525	

Discussion

This is a retrospective study.The study elaborated on the correlation between BUN and both short-term and long-term GV in elderly patients with T2DM were hospitalized. The results indicated a positive association, revealing that higher BUN were linked to greater short-term and long-term GV. In other words, baseline BUN not only serve as indicators for assessing short-term GV during hospitalization monitoring but also for evaluating annual long-term FPG-GV during community follow-ups. Therefore, applying this finding in clinical practice suggests that monitoring blood BUN can help connect short-term and long-term GV with the occurrence of diabetes-related complications. Thus, when blood BUN are elevated, it is essential to enhance the management of GV in elderly patients with T2DM promptly and conduct appropriate screening for diabetes-related complications to facilitate early identification, prevention, control, and mitigation of diabetes complications, thereby

Table 7 Subgroup Analysis of the Correlation Between BUN Levels and Long-Term GV

	Subgroup	β (95% CI)	*P*-value	*P* Interaction
FPG-SD	Age			0.565
	≥75	0.05 (0.02, 0.08)	0.002	
	<75	0.06 (0.02, 0.10)	0.001	
	Gender			0.865
	Female	0.05 (0.02, 0.09)	0.002	
	Male	0.06 (0.02, 0.09)	0.002	
	BMI			0.925
	<24	0.06 (0.01, 0.10)	0.010	
	≥24, <28	0.05 (0.02, 0.08)	0.002	
	≥28	0.06 (0.01, 0.10)	0.011	
	HbA1c			0.417
	<8.5	0.03 (−0.00, 0.07)	0.072	
	≥8.5	0.01 (−0.04, 0.06)	0.639	
FPG-CV	Age			0.609
	≥75	0.00 (0.00, 0.01)	0.024	
	<75	0.00 (0.00, 0.01)	0.013	
	Gender			0.361
	Female	0.00 (−0.00, 0.01)	0.059	
	Male	0.01 (0.00, 0.01)	0.006	
	BMI			0.736
	<24	0.01 (0.00, 0.01)	0.021	
	≥24, <28	0.00 (0.00, 0.01)	0.034	
	≥28	0.00 (−0.00, 0.01)	0.055	
	HbA1c			0.468
	<8.5	0.00 (−0.00, 0.01)	0.137	
	≥8.5	0.00 (−0.00, 0.01)	0.739	
FPG-ARV	Age			0.226
	≥75	0.49 (−0.05, 1.03)	0.076	
	<75	0.89 (0.27, 1.51)	0.005	
	Gender			0.650
	Female	0.56 (0.00, 1.13)	0.049	
	Male	0.71 (0.12, 1.30)	0.018	
	BMI			0.087
	<24	1.28 (0.53, 2.03)	0.001	
	≥24, <28	0.47 (−0.08, 1.02)	0.096	
	≥28	0.52 (−0.22, 1.27)	0.170	
	HbA1c			0.348
	<8.5	0.59 (−0.06, 1.24)	0.076	
	≥8.5	0.15 (−0.76, 1.06)	0.744	
FPG-VIM	Age			0.439
	≥75	0.09 (0.03, 0.15)	0.003	
	<75	0.12 (0.05, 0.19)	0.001	
	Gender			0.635
	Female	0.11 (0.05, 0.17)	0.001	
	Male	0.09 (0.03, 0.16)	0.006	
	BMI			0.909
	<24	0.09 (0.01, 0.17)	0.032	
	≥24, <28	0.11 (0.05, 0.17)	0.001	
	≥28	0.09 (0.01, 0.18)	0.027	
	HbA1c			0.878
	<8.5	0.03 (−0.03, 0.10)	0.272	
	≥8.5	0.04 (−0.05, 0.13)	0.349	

improving their quality of life.The study also examines the relationship between eGFR and short-term and long-term GV, but no correlation has been found between the two ($P > 0.05$).Therefore, in elderly patients with T2DM, BUN may be more effective than eGFR in reflecting and capturing changes in GV.

Previous studies have indicated that individuals with elevated BUN levels, regardless of their eGFR levels, have a significantly increased risk of incident diabetes mellitus in humans. However, there is no independent correlation between eGFR and the risk of incident diabetes mellitus.[18] Subsequently, Chinese scholars discovered that after adjusting for age and gender, both quartiles and continuous variables of BUN were significantly positively associated with an increased risk of T2DM. Even after adjusting for eGFR, lipid levels, blood pressure, and BMI, the correlation persisted. Furthermore, it was noted that this association was more pronounced among individuals with lower BMI.[17] Some scholars have pointed out the association between the levels and ratios of plasma BUN cycle-related amino acids and the occurrence of T2DM in Chinese adults,[28] One of the potential reasons for the significant role of BUN in the development of T2DM.Elevated levels of BUN are associated with an increased risk of insulin use in patients with T2DM. This indicates that as blood BUN levels rise, patients may face greater challenges in controlling blood glucose levels, suggesting that high BUN levels could lead to increased GV.[19] Therefore, the elevation of blood BUN levels not only increases the risk of developing diabetes but may also exacerbate GV in patients with diabetic. The findings of this study are consistent with the aforementioned findings.

The association between BUN and increased risk of incident diabetes mellitus in humans is more pronounced in younger patients. Additionally, the correlation between the two can vary depending on race. In individuals of African descent, there is a stronger correlation between high BUN levels and increased risk of incident diabetes mellitus. This suggests that in patients across different BMI categories, excluding those who are obese, the increased risk of incident diabetes mellitus with elevated BUN levels.[18] Some scholars have pointed out that there are differences in the correlation between BMI and the risk of T2DM among different racial populations.[29] In middle- and low-income countries, there is a significant variation in the association between BMI and the risk of incident diabetes mellitus, with younger age and lower BMI patients showing a significantly increased risk of diabetes.[30] Therefore, the differences in race, age, and BMI may affect the correlation between BUN and the risk of incident T2DM. Based on this, we can hypothesize that the differences in race, age, and BMI may have an impact on the correlation between BUN and short-term and long-term GV. This study found that the correlation between BUN and GV is stable among different gender, age, BMI, and HbA1c subgroups.

The evaluation of GV in patients with T2DM is extremely important in clinical practice, and more investigations are currently underway to figure out the clinical value and adverse effects of blood glucose fluctuations.

Previous studies have indicated that TIR, DR, DN, and CAN are all significantly negatively correlated.[6] Furthermore, even after adjusting for parameters such as SD, MAGE, CV, as well as baseline factors like age, gender, and duration of diabetes, the above correlations still exist. This means that the correlation between TIR and microvascular complications is not influenced by other GV parameters.[6,31,32] TIR is not only associated with the aforementioned microvascular changes, but also significantly negatively correlated with cardiovascular complications and increased risk of all-cause mortality.[7] Lee et al, have shown that long-term fluctuations in FPG, FPG-VIM, FPG-SD, FPG-CV and FPG-ARV are associated with the risk of stroke, myocardial infarction, and all-cause mortality in patients with diabetes, and are not influenced by glucose-lowering medications, average fasting blood glucose levels, and metabolic risk factors.[33] Therefore, it can be seen that the correlation between long-term and short-term GV and diabetes complications is not completely the same. The same GV parameter may be associated with multiple different diabetes complications, while multiple different GV parameters may be associated with the same type of diabetes complication.This could be the reason why there is a difference in the correlation between BUN and multiple parameters of long-term and short-term GV in elderly patients with T2DM.

This study also has certain limitations.First, it is important to note that our study primarily focuses on the residents of Kunshan City, Suzhou City, Jiangsu Province. Therefore, there may be a selection bias present in our research. Secondly, the use of antidiabetic medications or insulin therapy during the follow-up period may have an impact on GV in elderly patients with T2DM. Thirdly, although we have adjusted for some potential confounding factors, there may still be other confounding factors at play. Moreover, it is worth mentioning that elderly patients with T2DM are included in the study only if they had overall annually FPG measures at community hospitals during the follow-up period that were equivalent to or greater than three times.This means that not every subject underwent the examination of FPG at every follow-up

visit, and this unequal distribution of elderly patients with T2DM may have influenced the results.These factors could potentially affect the correlation between BUN and short-term and long-term GV.

This study has certain Advantages.Most studies are unable to obtain long-term FPG parameters from patients. While the monitoring of FPG levels is unaffected by these factors, laboratory testing of HbA1c levels can be impacted by anemia, chronic kidney disease, age, medication, race, and hemoglobin disorders.[34] They can only use HbA1c to represent the long-term GV of patients for 2–3 months. However, in this study, FPG were collected annually during the follow-up period to represent long-term GV. This study investigated long-term GV over

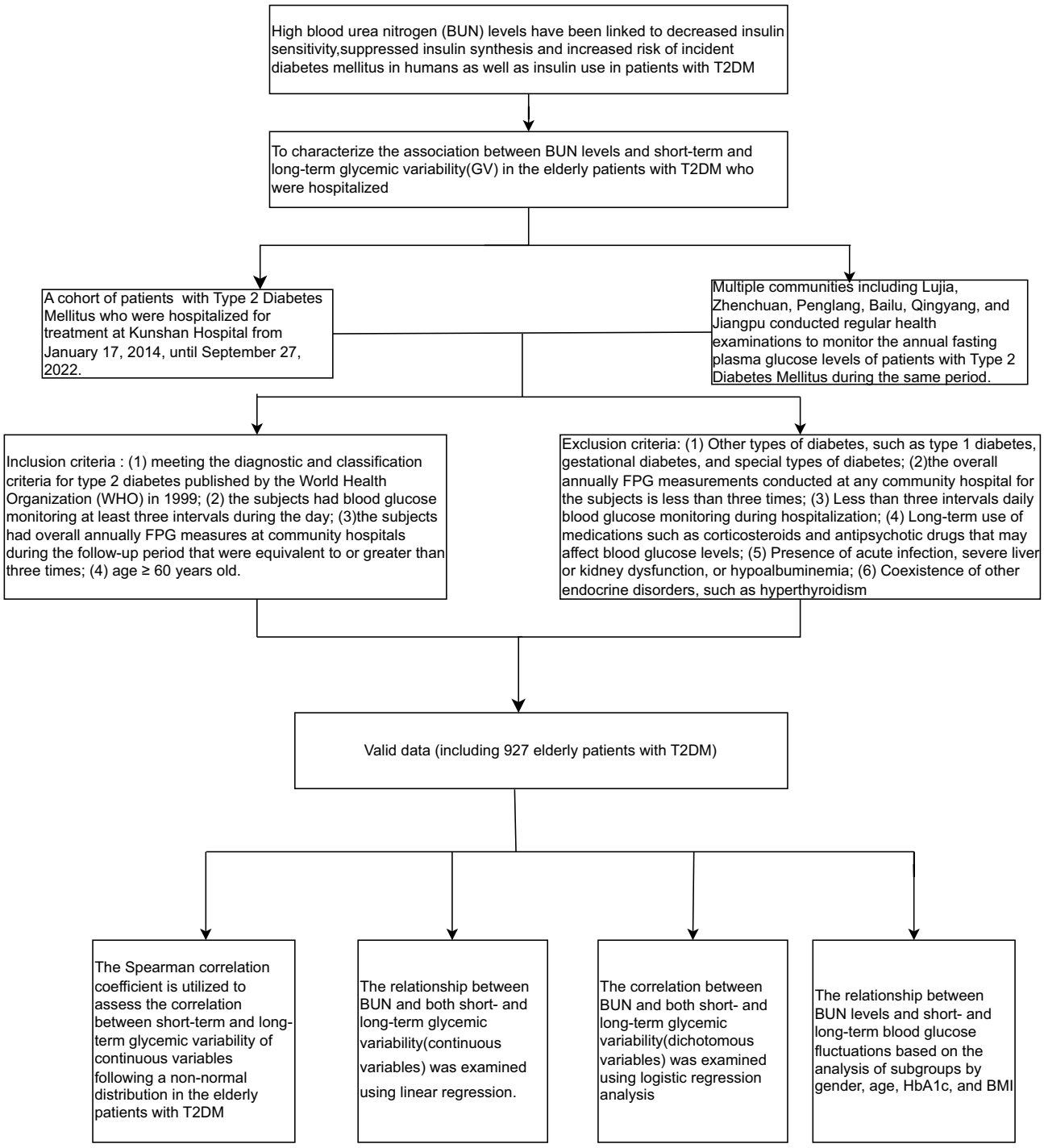

Figure 1 Research Design Process Diagram.

a longer period of time. Additionally, the gender ratio in this study was relatively balanced and the large sample size and long follow-up time increased the reliability of the results.

Conclusion and Future Prospects

In conclusion, this study found that elevated BUN levels in elderly patients with T2DM were hospitalized are positively correlated with both short- and long-term GV. This means that higher blood BUN levels are associated with greater short- and long-term GV. Therefore, BUN levels in elderly patients with T2DM were hospitalized can be indicative of and used to assess short-term GV and long-term FPG-GV, which is crucial for guiding GV management in clinical practice.

We have ultimately summarized the research design process diagram of this article, as illustrated in Figure 1.

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Disclosure

The authors declare no conflicts of interest related to this work.

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