


# Higher Clinical Frailty Scale is Associated with Higher Visit-to-Visit Glycated Hemoglobin (HbA1c) Variability in Patients with Type 2 Diabetes Mellitus: A Propensity Score-Matched Study

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**Objective:** Patients with type 2 diabetes mellitus (T2DM) have high risk of frailty. The clinical frailty scale (CFS) has been used to evaluate clinical frailty. To evaluate the association between CFS and visit-to-visit glycated hemoglobin (HbA1C) variability in T2DM patients.

**Methods:** Patients who were hospitalized with T2DM and received at least three HbA1C tests after discharging from endocrinology department and general practice department during 12-month follow-up were retrospectively enrolled. The patients were divided into the low-HbA1C variability group and the high-HbA1C variability group according to the results of the HbA1C variability score (HVS). The baseline clinical information, including CFS during hospitalization, was collected and compared between the two groups. We performed a propensity score match (PSM) to eliminate the influences of other confounding factors.

**Results:** A total of 370 patients were included in this study. Most baseline demographic, clinical parameters and metabolic parameters were comparable between the two groups except age, baseline HbA1C, albumin, and comorbidities including hypertension and dyslipidemia between the two groups before PSM. All of the relative parameters were comparable after a 1:1 PSM. Uni-variable and multi-variable logistic analysis revealed that higher CFS was associated with higher HbA1C variability and receiver operating characteristic curve showed that CFS had good predictive value in HVS.

**Conclusion:** Higher CFS was associated with higher visit-to-visit HbA1C variability.

**Keywords:** clinical frailty scale, HbA1C variability score, type 2 diabetes mellitus, propensity score match

## Background

With the rapidly increasing prevalence of type 2 diabetes mellitus (T2DM) during the past few decades, the epidemic of this disorder has become a serious concern in modern society worldwide.<sup>1</sup> International guidelines highlight the importance of proper management of blood glucose in patients with T2DM.<sup>2,3</sup> Lately, the “low and stable” strategy in managing T2DM has been recognized.<sup>4</sup> Visit-to-visit glycemic variability (including blood glucose and HbA1C variability) has been acknowledged as a risk factor for higher mortality and disability rates for T2DM patients.<sup>5–9</sup> Hence, these patients are at high risk of unfavorable clinical outcomes and need more attention in clinical practice.

However, we did not get any reports regarding the risk factors for high visit-to-visit glycemic variability even though previous studies have issued that age, food intake, exercise, medication usage, treatment compliance, and comorbidities are all associated with glycemic variability.<sup>10–12</sup>

Frailty, which has a high prevalence in patients with T2DM, has been demonstrated to be associated with a worse prognosis of different medical conditions.<sup>13–17</sup> For patients with T2DM, frailty was associated with worse clinical outcomes, especially for older people.<sup>18,19</sup> The underlying mechanism of frailty in T2DM patients is complicated.

Previous studies show that malnutrition and sarcopenia are potential mechanism of frailty in these patients.<sup>20,21</sup> The compromised skeletal muscle function, vascular function are also related to frailty in T2DM patients.<sup>22</sup> High glycemic variability has been demonstrated to be a risk factor for frailty. In a pilot study using continuous glucose monitoring, T2DM patients were divided into frailty patients and non-frailty patients, after multivariate adjustments, the post-lunch time above range was associated with higher risk of frailty.<sup>23</sup> This study showed the potential relationship between glycemic variability and frailty.

In clinical practice, the evaluation of frailty often needs a comprehensive history and physical examination. Lately, the clinical frailty scale (CFS), which is a simple scoring system, is introduced and shows good clinical value in evaluating frailty.<sup>24,25</sup>

In this study, we aim to evaluate the association between CFS and visit-to-visit HbA1C variability in patients with T2DM.

## Materials and Methods

This is a single-center retrospective study. T2DM patients hospitalized in endocrinology department and general practice department from January 1, 2018, to December 31, 2022, were enrolled. Patients with acute diabetic complications, patients younger than 18 years old; patients with other types of DM, patients with severe cerebrovascular diseases, cognitive impairment, acute coronary syndrome, infection, tumor, and severe hepatic and renal dysfunction were excluded. Patients with missing clinical data and patients who refused to or could not participate in our study (CFS $\geq$ 8) were excluded. Patients who did not have at least three HbA1C test results during 12-month follow-up were also excluded.

The baseline demographic and clinical information including CFS were collected. The on-admission and follow-up laboratory test results were also collected. Blood samples were analyzed by Sysmex XE2100 automatic blood analyzer from Donga Company, Japan; biochemical function (hs-CRP, liver function, kidney function, lipid profile, blood glucose, etc).

The CFS is a 9-point scale, which has been detailed and illustrated elsewhere. All patients were evaluated by trained nurses on admission and the CFS results were extracted from electrical medical records.

HbA1c was measured in whole blood using turbidimetric inhibition immuno assay by Siemens DCA vantage analyzer. The HbA1c variability score (HVS) developed by Forbes A. et al in 2018, was used to evaluate the visit-to-visit variability of HbA1C in our study. The HVS is the frequency of 0.5% (5.5 mmol/mol) change in the first three HbA1c results during clinical follow-up when compared with baseline HbA1C (the value of HbA1C during hospitalization).<sup>26</sup> Patients were divided into the high HbA1C variability group (HVS  $\geq$  2) and the low HbA1c group (HVS  $\leq$  1) according to the HVS results.

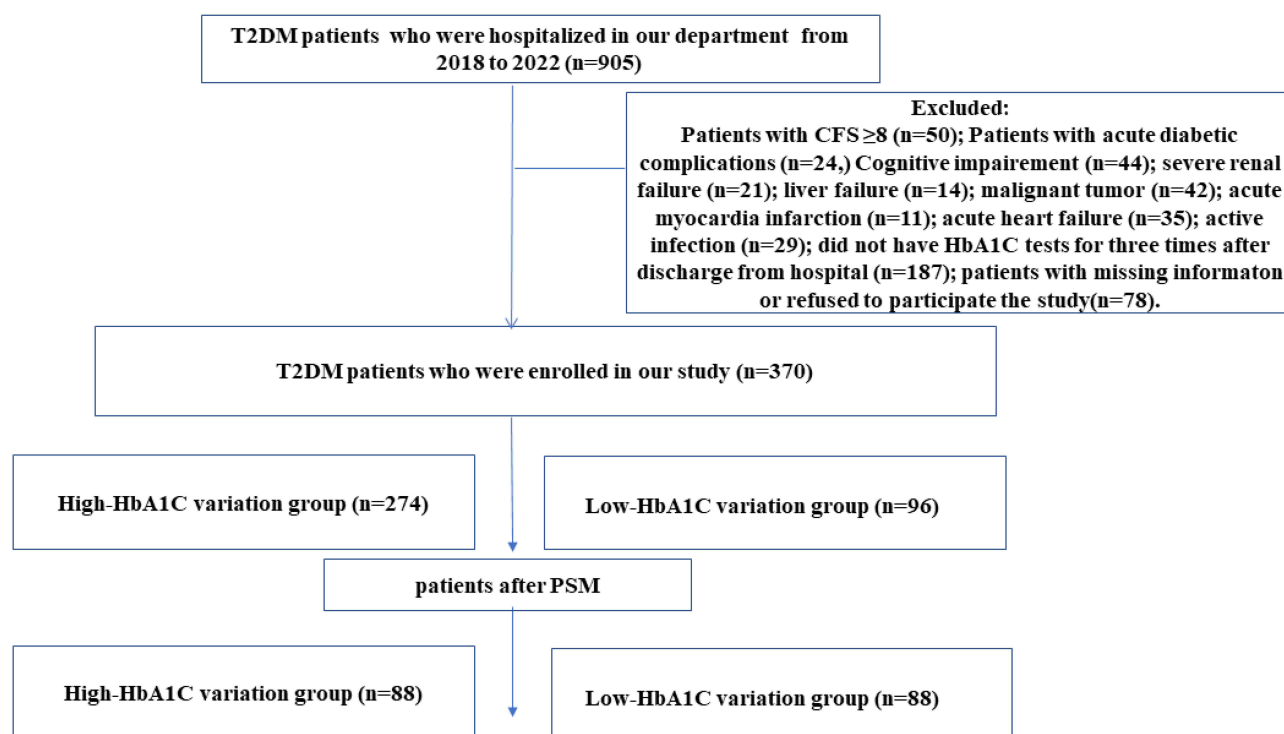
All of the enrolled patients and their family members provided informed consent. This study was approved by the ethics committee of Beijing Tongren Hospital, Capital Medical University and it fully met the requirements of the Helsinki Declaration for clinical research.

## Statistical Analysis

Categorical variables were presented as numbers and frequencies (percentages) and were compared using the chi-square test or exact Fisher test, as appropriate. Continuous variables were expressed as mean SD  $\pm$  mean or median (quartile 1, quartile 3) based on normality assumption and were compared using the independent sample *t*-test or Mann–Whitney test, as appropriate. A logistic regression model with propensity scores matching (PSM) of a 1:1 ratio was performed with variables associated with HVS to balance the patient characteristics between the two groups. The predictive value of CFS in HVE was evaluated by the receiver operating characteristic (ROC) curve. Data processing and analysis were performed using R version 4.4.0 (2024-04-24), along with Zstats 1.0 ([www.zstats.net](http://www.zstats.net)).

## Results

A total of 370 patients were enrolled, 274 patients were in the high-HbA1C variability group and 96 patients were in the low-HbA1C variability group (Figure 1).



**Figure 1** Study flow chart.

The comparison results of baseline demographic and clinical data before PSM were shown in Table 1 and Table 2: Most of the parameters between the two groups were comparable except that patients in the high-HbA1C variability group were older [66.00 (52.00, 77.00) vs 61.50 (47.00, 72.25), years,  $p = 0.032$ ], the medical history of T2DM were

**Table 1** Comparison Results of Demographic and Clinical Parameters Between the Two Groups Before PSM

Variable	Total (n = 370)	Low- HbA1C Variability Group (n = 96)	High- HbA1C Variability Group (n = 274)	Statistic	P	SMD
Age, years, M (Q <sub>1</sub> , Q <sub>3</sub> )	65.50 (51.00, 75.75)	61.50 (47.00, 72.25)	66.00 (52.00, 77.00)	Z=-2.150	<b>0.032</b>	0.263
Gender, n (%)				$\chi^2=0.027$	0.903	
Female	140 (37.84)	37 (38.54)	103 (37.59)			0.027
Male	230 (61.89)	59 (61.46)	171 (62.40)			
Medical history length of T2DM, years, M (Q <sub>1</sub> , Q <sub>3</sub> )	10.00 (7.00, 13.00)	8.00 (6.00, 12.00)	10.00 (7.25, 13.00)	Z=-3.352	<b>&lt;0.001</b>	0.351
Insulin usage, n (%)				$\chi^2=0.100$	0.752	
No	136 (36.76)	34 (35.42)	102 (37.23)			0.037
Yes	234 (63.24)	62 (64.58)	172 (62.77)			-0.037
CVD, n (%)				$\chi^2=0.875$	0.350	
Yes	288 (77.84)	78 (81.25)	210 (76.64)			-0.109
No	82 (22.16)	18 (18.75)	64 (23.36)			0.109

(Continued)

**Table 1** (Continued).

Variable	Total (n = 370)	Low- HbA1C Variability Group (n = 96)	High- HbA1C Variability Group (n = 274)	Statistic	P	SMD
CAD, n (%)				$\chi^2=0.035$	0.852	
Yes	261 (70.54)	67 (69.79)	194 (70.80)			0.022
No	109 (29.46)	29 (30.21)	80 (29.20)			-0.022
Hypertension, n (%)				$\chi^2=5.307$	<b>0.021</b>	
Yes	105 (28.38)	36 (37.50)	69 (25.18)			-0.284
No	265 (71.62)	60 (62.50)	205 (74.82)			0.284
CKD, n (%)				$\chi^2=0.009$	0.923	
Yes	195 (52.7)	51 (53.12)	144 (52.55)			-0.011
No	175 (47.3)	45 (46.88)	130 (47.45)			0.011
Dyslipidemia, n (%)				$\chi^2=8.430$	<b>0.004</b>	
Yes	52 (14.05)	22 (22.92)	30 (10.95)			-0.383
No	318 (85.95)	74 (77.08)	244 (89.05)			0.383
Smoking, n (%)				$\chi^2=1.649$	0.199	
Yes	195 (52.7)	56 (58.33)	139 (50.73)			-0.152
No	175 (47.3)	40 (41.67)	135 (49.27)			0.152
Alcoholic, n (%)				$\chi^2=0.613$	0.434	
Yes	310 (83.78)	78 (81.25)	232 (84.67)			0.095
No	60 (16.22)	18 (18.75)	42 (15.33)			-0.095
BMI, M (Q <sub>1</sub> , Q <sub>3</sub> )	23.00 (21.00, 25.50)	22.70 (20.90, 24.90)	23.20 (21.10, 25.70)	Z=-1.010	0.313	0.101
Anti-platelet therapy, n (%)				$\chi^2=0.333$	0.564	
Yes	55 (14.86)	16 (16.67)	39 (14.23)			-0.070
No	315 (85.14)	80 (83.33)	235 (85.77)			0.070
ACEi or ARB, n (%)				$\chi^2=0.000$	0.987	
Yes	166 (44.86)	43 (44.79)	123 (44.89)			0.002
No	204 (55.14)	53 (55.21)	151 (55.11)			-0.002
$\beta$ Blocker, n (%)				$\chi^2=0.229$	0.632	
Yes	212 (57.3)	57 (59.38)	155 (56.57)			-0.057
No	158 (42.7)	39 (40.62)	119 (43.43)			0.057
CCB, n (%)				$\chi^2=0.408$	0.523	
Yes	275 (74.32)	69 (71.88)	206 (75.18)			0.077
No	95 (25.68)	27 (28.12)	68 (24.82)			-0.077
Diuretic, n (%)				$\chi^2=0.007$	0.934	
Yes	294 (79.46)	76 (79.17)	218 (79.56)			0.010
No	76 (20.54)	20 (20.83)	56 (20.44)			-0.010

(Continued)

**Table 1** (Continued).

Variable	Total (n = 370)	Low- HbA1C Variability Group (n = 96)	High- HbA1C Variability Group (n = 274)	Statistic	P	SMD
Statins, n (%)				$\chi^2=0.180$	0.672	
Yes	51 (13.78)	12 (12.50)	39 (14.23)			0.050
No	319 (86.22)	84 (87.50)	235 (85.77)			-0.050

**Notes:** \*bold font indicates statistically significance.

**Abbreviations:** PSM, propensity score-matched method; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; CVD, cerebrovascular disease; CKD, chronic kidney disease; HbA1C, Hemoglobin A1C; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker.

**Table 2** Comparison Results of Laboratory Parameters Between the Two Groups Before PSM

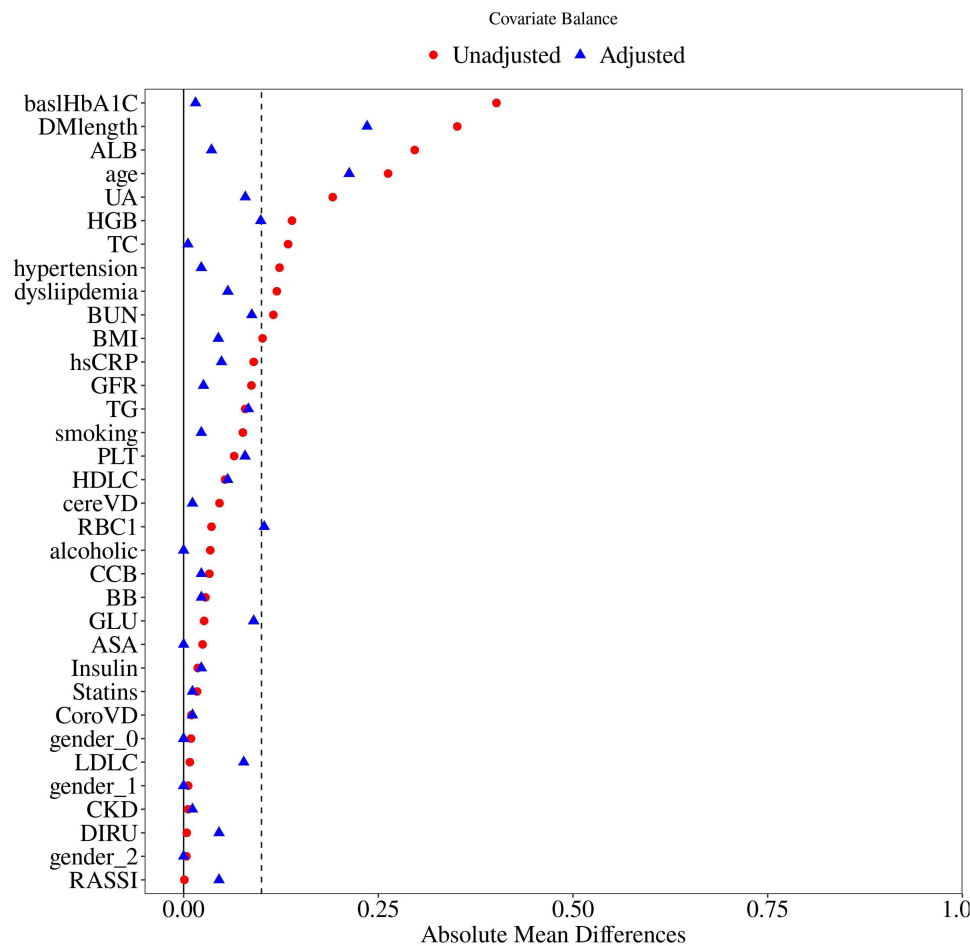
Variable	Total (n = 370)	Low- HbA1C Variability Group (n = 96)	High- HbA1C Variability Group (n = 274)	Statistic	P	SMD
eGFR, mL/min, Mean $\pm$ SD	73.71 $\pm$ 14.68	74.64 $\pm$ 15.38	73.39 $\pm$ 14.44	$t=0.722$	0.471	-0.087
Albumin, g/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	41.20 (38.05, 43.70)	42.20 (39.77, 44.50)	41.00 (38.00, 43.30)	$Z=-2.456$	<b>0.014</b>	-0.297
Uric acid, mmol/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	402.00 (318.00, 455.75)	377.00 (310.00, 439.75)	406.00 (323.75, 462.00)	$Z=-1.946$	0.052	0.192
Fast glucose, mmol/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	9.42 (8.50, 11.87)	9.30 (8.20, 11.85)	9.50 (8.60, 11.87)	$Z=-0.587$	0.557	-0.026
Baseline HbA1C, %, M (Q <sub>1</sub> , Q <sub>3</sub> )	8.40 (7.90, 9.10)	8.10 (7.80, 8.50)	8.50 (7.90, 9.10)	$Z=-3.524$	<b>&lt;0.001</b>	0.402
hs-CRP, g/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	7.50 (5.32, 9.40)	7.70 (5.80, 9.75)	7.50 (5.30, 9.40)	$Z=-0.883$	0.377	-0.090
RBC, 10 <sup>12</sup> /L, M (Q <sub>1</sub> , Q <sub>3</sub> )	4.50 (3.80, 5.20)	4.45 (3.77, 5.10)	4.50 (3.80, 5.20)	$Z=-0.409$	0.683	0.036
Hemoglobin, g/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	126.00 (115.25, 138.00)	127.00 (118.00, 138.75)	126.00 (115.00, 137.75)	$Z=-1.209$	0.227	-0.139
Platelets, 10 <sup>9</sup> /L, M (Q <sub>1</sub> , Q <sub>3</sub> )	203.00 (151.50, 241.00)	204.00 (167.25, 240.25)	201.00 (150.25, 241.00)	$Z=-0.424$	0.672	-0.065
TC, mmol/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	4.69 (4.31, 5.30)	4.85 (4.44, 5.46)	4.67 (4.27, 5.28)	$Z=-1.579$	0.114	-0.134
TG, mmol/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	2.23 (1.76, 2.60)	2.17 (1.85, 2.54)	2.25 (1.70, 2.64)	$Z=-0.431$	0.667	0.079
HDL-C, mmol/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	0.97 (0.87, 1.29)	0.98 (0.88, 1.31)	0.96 (0.86, 1.27)	$Z=-0.568$	0.570	-0.053
LDL-C, mmol/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	3.01 (2.53, 3.42)	3.12 (2.64, 3.40)	2.96 (2.51, 3.45)	$Z=-0.705$	0.481	0.008

**Notes:** \*bold font indicates statistically significance.

**Abbreviations:** PSM, propensity score-matched method; eGFR, estimated glomerular filtration rate; HbA1C, Hemoglobin A1C; hs-CRP, hypersensitive C-reactive protein; TC, total cholesterol; TG, total triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

longer [10.00 (7.25, 13.00) vs 8.00 (6.00, 12.00), years,  $p < 0.001$ ], the CFS were higher [5.00 (3.25, 6.00) vs 3.00 (2.00, 4.00),  $p < 0.001$ ], the proportion of hypertension was higher (74.82% vs 62.50%,  $p = 0.021$ ), and the proportion of dyslipidemia was higher (89.05% vs 77.08%,  $p = 0.004$ ), and the level of serum albumin was lower [41.00 (38.00, 43.30) vs 42.20 (39.77, 44.50), g/L,  $p = 0.014$ ], the level of baseline HbA1C were higher [8.50 (7.90, 9.10) vs 8.10 (7.80, 8.50), %,  $p < 0.001$ ].

We further performed PSM to reduce the potential influences of other covariates. The detailed PSM process is shown in Figure 2. In conclusion, after a 1:1 ratio PSM, there was no significant difference between the two groups regarding relative parameters after PSM (Tables 3 and 4).



**Figure 2** The process of propensity score-matched analysis.

Both the uni-variable and multi-variable logistic analysis between the two groups after PSM were performed and the results were shown in Table 5: The CFS was the independent risk factor for high HVS (OR = 2.05 95% CI (1.62 ~ 2.61),  $p < 0.001$ ).

**Table 3** Comparison Results of Demographic and Clinical Parameters Between the Two Groups After PSM#

Variable	Total (n = 176)	Low- HbA1C Variability Group (n = 88)	High- HbA1C Variability Group (n = 88)	Statistic	P	SMD
Age, M (Q <sub>1</sub> , Q <sub>3</sub> )	65.00 (48.00, 75.00)	62.50 (47.75, 74.00)	66.00 (51.25, 77.00)	Z=-1.379	0.168	0.209
Gender, n (%)				$\chi^2=0.000$	1.000	
No	66 (37.5)	33 (37.50)	33 (37.50)			0.000
Yes	110 (62.5)	55 (62.50)	55 (62.50)			0.000
Medical history length of T2DM, years, M (Q <sub>1</sub> , Q <sub>3</sub> )	9.00 (7.00, 13.00)	9.00 (6.00, 12.00)	10.00 (7.00, 13.00)	Z=-1.758	0.079	0.240
Insulin usage, n (%)				$\chi^2=0.096$	0.757	
No	68 (38.64)	33 (37.50)	35 (39.77)			0.046
Yes	108 (61.36)	55 (62.50)	53 (60.23)			-0.046

(Continued)

**Table 3** (Continued).

Variable	Total (n = 176)	Low- HbA1C Variability Group (n = 88)	High- HbA1C Variability Group (n = 88)	Statistic	P	SMD
CAD, n (%)				$\chi^2=0.036$	0.850	
No	141 (80.11)	70 (79.55)	71 (80.68)			0.029
Yes	35 (19.89)	18 (20.45)	17 (19.32)			-0.029
CVD, n (%)				$\chi^2=0.026$	0.871	
No	121 (68.75)	60 (68.18)	61 (69.32)			0.025
Yes	55 (31.25)	28 (31.82)	27 (30.68)			-0.025
Hypertension, n (%)				$\chi^2=0.101$	0.750	
No	60 (34.09)	31 (35.23)	29 (32.95)			-0.048
Yes	116 (65.91)	57 (64.77)	59 (67.05)			0.048
CKD, n (%)				$\chi^2=0.023$	0.880	
No	89 (50.57)	45 (51.14)	44 (50.00)			-0.023
Yes	87 (49.43)	43 (48.86)	44 (50.00)			0.023
Dyslipidemia, n (%)				$\chi^2=0.979$	0.322	
No	31 (17.61)	18 (20.45)	13 (14.77)			-0.160
Yes	145 (82.39)	70 (79.55)	75 (85.23)			0.160
Smoking, n (%)				$\chi^2=0.094$	0.759	
No	104 (59.09)	51 (57.95)	53 (60.23)			0.046
Yes	72 (40.91)	37 (42.05)	35 (39.77)			-0.046
Alcoholic, n (%)				$\chi^2=0.000$	1.000	
No	146 (82.95)	73 (82.95)	73 (82.95)			0.000
Yes	30 (17.05)	15 (17.05)	15 (17.05)			0.000
BMI, M (Q1, Q3)	22.71 (20.80, 25.50)	22.70 (20.88, 24.95)	22.90 (20.75, 25.83)	Z=-0.317	0.752	0.043
Antiplatelet therapy, n (%)				$\chi^2=0.000$	1.000	
No	26 (14.77)	13 (14.77)	13 (14.77)			0.000
Yes	150 (85.23)	75 (85.23)	75 (85.23)			0.000
ACEi or ARB, n (%)				$\chi^2=0.371$	0.543	
No	76 (43.18)	40 (45.45)	36 (40.91)			-0.092
Yes	100 (56.82)	48 (54.55)	52 (59.09)			0.092
$\beta$ Blocker, n (%)				$\chi^2=0.093$	0.761	
No	100 (56.82)	51 (57.95)	49 (55.68)			-0.046
Yes	76 (43.18)	37 (42.05)	39 (44.32)			0.046
CCB, n (%)				$\chi^2=0.115$	0.735	
No	128 (72.73)	63 (71.59)	65 (73.86)			0.052
Yes	48 (27.27)	25 (28.41)	23 (26.14)			-0.052

(Continued)

**Table 3** (Continued).

Variable	Total (n = 176)	Low- HbA1C Variability Group (n = 88)	High- HbA1C Variability Group (n = 88)	Statistic	P	SMD
Diuretic, n (%)				$\chi^2=0.485$	0.486	
No	132 (75)	68 (77.27)	64 (72.73)			-0.102
Yes	44 (25)	20 (22.73)	24 (27.27)			0.102
Statins, n (%)				$\chi^2=0.050$	0.823	
No	23 (13.07)	11 (12.50)	12 (13.64)			0.033
Yes	153 (86.93)	77 (87.50)	76 (86.36)			-0.033

**Notes:** #The following variables were used in the propensity score (PSM) model: age, sex, medical history of diabetes, hypertension, dyslipidemia, BMI, previous history of coronary artery disease, cerebrovascular disease, smoking, hypertension, CKD, previous use of antiplatelet therapy, ACEI or ARB,  $\beta$ -blockers, statins. \*Red font indicates statistically significance.

**Abbreviations:** PSM, propensity score-matched method; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; CVD, cerebrovascular disease; CKD, chronic kidney disease; BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker. CCB, calcium channel blocker.

**Table 4** Comparison Results of Laboratory Parameters Between the Two Groups After PSM#

Variable	Total (n = 176)	Low- HbA1C Variability Group (n = 88)	High- HbA1C Variability Group (n = 88)	Statistic	P	SMD
eGFR, mL/min, Mean $\pm$ SD	73.48 $\pm$ 14.79	73.66 $\pm$ 15.32	73.29 $\pm$ 14.33	t=0.165	0.870	-0.026
Albumin, g/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	42.00 (38.95, 44.35)	42.00 (38.95, 44.52)	42.05 (39.03, 44.23)	Z=-0.287	0.774	-0.035
Uric acid, mmol/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	380.50 (310.75, 445.50)	377.00 (310.75, 439.75)	392.50 (315.25, 461.00)	Z=-0.555	0.579	0.080
Fast glucose, mmol/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	9.55 (8.60, 12.33)	9.35 (8.43, 12.35)	9.60 (8.70, 12.25)	Z=-1.033	0.302	0.083
Baseline HbA1C, %, M (Q <sub>1</sub> , Q <sub>3</sub> )	8.20 (7.80, 8.60)	8.20 (7.88, 8.50)	8.20 (7.70, 8.72)	Z=-0.391	0.695	-0.018
hs-CRP, g/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	7.65 (5.80, 9.90)	7.70 (5.97, 9.75)	7.45 (5.75, 9.90)	Z=-0.577	0.564	-0.047
RBC, 10 <sup>12</sup> /L, M (Q <sub>1</sub> , Q <sub>3</sub> )	4.50 (3.80, 5.20)	4.50 (3.77, 5.10)	4.50 (3.90, 5.20)	Z=-0.758	0.448	0.106
Hemoglobin, g/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	127.00 (117.00, 140.25)	128.00 (119.00, 141.00)	126.50 (116.00, 139.25)	Z=-0.724	0.469	-0.095
Platelets, 10 <sup>9</sup> /L, M (Q <sub>1</sub> , Q <sub>3</sub> )	205.00 (168.75, 241.75)	202.00 (148.50, 237.00)	213.00 (177.00, 244.25)	Z=-0.886	0.375	0.083
TC, mmol/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	4.78 (4.31, 5.42)	4.85 (4.40, 5.42)	4.72 (4.26, 5.42)	Z=-0.450	0.653	-0.005
TG, mmol/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	2.17 (1.83, 2.52)	2.17 (1.87, 2.57)	2.16 (1.69, 2.48)	Z=-0.913	0.361	-0.085
HDL-C, mmol/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	0.98 (0.88, 1.33)	0.98 (0.88, 1.35)	0.98 (0.88, 1.31)	Z=-0.155	0.877	0.050
LDLC, mmol/L, M (Q <sub>1</sub> , Q <sub>3</sub> )	3.12 (2.57, 3.49)	3.13 (2.64, 3.42)	3.02 (2.56, 3.54)	Z=-0.012	0.991	0.071

**Notes:** #The following variables were used in the propensity score (PSM) model: age, sex, medical history of diabetes, hypertension, dyslipidemia, BMI, previous history of coronary artery disease, cerebrovascular disease, smoking, hypertension, CKD, previous use of antiplatelet therapy, ACEI or ARB,  $\beta$ -blockers, statins. \*Red font indicates statistically significance.

**Abbreviations:** PSM, propensity score-matched method; eGFR, estimated glomerular filtration rate; HbA1C, Hemoglobin A1C; hs-CRP, hypersensitive C-reactive protein; TC, total cholesterol; TG, total triglyceride; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

**Table 5** Results of Uni-Variable and Multi-Variable Logistic Analysis in Predicting HVS After PSM

Variable	Uni-Variable Analysis					Multi-Variable Analysis				
	$\beta$	S.E	t	P	OR (95% CI)	$\beta$	S.E	t	P	OR (95% CI)
Hypertension										
No					1.00 (Reference)					1.00 (Reference)
Yes	0.10	0.32	0.32	0.750	1.11 (0.59 ~ 2.06)	0.23	0.37	0.63	0.529	1.26 (0.61 ~ 2.59)

(Continued)



Table 5 (Continued).

Variable	Uni-Variable Analysis					Multi-Variable Analysis				
	$\beta$	S.E	t	P	OR (95% CI)	$\beta$	S.E	t	P	OR (95% CI)
Dyslipidemia										
No					1.00 (Reference)					1.00 (Reference)
Yes	0.39	0.40	0.99	0.324	1.48 (0.68 ~ 3.25)	0.85	0.47	1.79	0.073	2.33 (0.92 ~ 5.90)
Baseline HbA1C	-0.03	0.20	-0.13	0.898	0.97 (0.66 ~ 1.44)	-0.24	0.24	-1.00	0.315	0.79 (0.49 ~ 1.26)
Albumin	-0.01	0.04	-0.23	0.818	0.99 (0.92 ~ 1.07)	-0.01	0.04	-0.12	0.904	0.99 (0.91 ~ 1.08)
CFS	0.68	0.12	5.82	<b>&lt;0.001</b>	1.97 (1.57 ~ 2.47)	0.72	0.12	5.89	<b>&lt;0.001</b>	2.05 (1.62 ~ 2.61)
Age	0.01	0.01	1.39	0.165	1.01 (0.99 ~ 1.04)	0.00	0.01	0.22	0.826	1.00 (0.97 ~ 1.03)
Medical history length of T2DM	0.05	0.03	1.64	0.101	1.05 (0.99 ~ 1.11)	0.03	0.04	0.80	0.423	1.03 (0.95 ~ 1.12)

Notes: \*bold indicates statistically significance.

Abbreviations: HVS, HbA1C variability score; PSM, propensity score-matched method; OR: Odds Ratio; CI, Confidence Interval; CFS, clinical frailty scale.

The predictive value of CFS in HVS was further evaluated by using the ROC curve and the result showed that CFS had good predictive value in predicting HVS [AUC = 0.774, 95% CI: (0.705 to 0.833),  $p < 0.001$ ], the cut-off value of HVS was 4.0 with sensitivity = 63.64% and specificity = 79.55% (Figure 3).

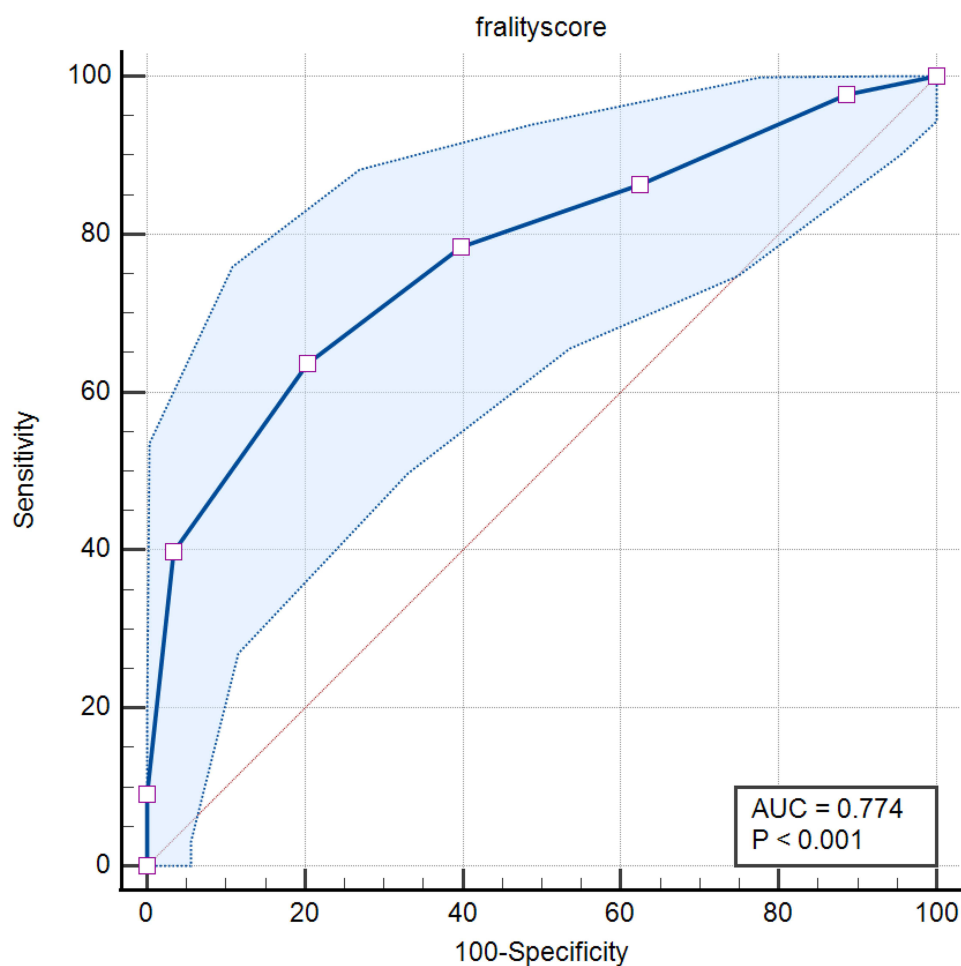


Figure 3 Results of the receiver operating characteristic curve.

## Discussion

The association between high visit-to-visit HbA1C variability in T2DM patients and adverse clinical outcomes has been well-recognized. However, studies that explore the risk factors for the visit-to-visit HbA1C variability are scarce. So far as we know, our study is the first study evaluating the association between CFS and visit-to-visit HbA1C variability in T2DM patients. Our study revealed that higher CFS was associated with higher visit-to-visit HbA1C variability in patients with T2DM.

T2DM, one of the most common metabolic disorders, contributes to the mortality and disability in millions of people worldwide by causing macro-vascular (ischemia heart disease stroke, etc) and micro-vascular (including blindness, lower limb amputation and renal failure, etc) complications.<sup>27,28</sup> The underlying mechanism of the complications caused by T2DM is complex, insulin resistance, inflammation, oxidized stress, mitochondrial dysfunction, and endothelial dysfunction are all believed to be associated with the development of T2DM-related complications.<sup>1,2,28–30</sup>

Higher visit-to-visit glycemia variability was demonstrated to be associated with these pathology changes of T2DM. Xu Jet al included 1856 community residents without T2DM and all of the participants received tests for insulin resistance evaluation by using the homeostatic model assessment. A total of 153 (8.2%) participants developed T2DM during follow-up and high visit-to-visit fasting plasma glucose variability was associated with a 1.48 increased risk of diabetes after adjusting other covariates. Further mediation analyses suggested that changes in insulin resistance might mediate 17.3% of the association between increased visit-to-visit fasting plasma glucose variability and elevated diabetes risk. This study demonstrated high visit-to-visit fasting plasma glucose variability was associated with increased insulin resistance.<sup>31</sup> The association between visit-to-visit glycemia variability and oxidative stress was also confirmed in a study by Saito Y et al which explored the association between visit-to-visit HbA1C variability and cancer development in T2DM patients.<sup>32</sup> Fang Q et al who demonstrated that long-term visit-to-visit HbA1c variability was independently associated with aortic stiffness progression in T2DM patients.<sup>5</sup>

Frailty is a common condition in patients with chronic diseases, especially in aged people.<sup>13</sup> T2DM patients are at high risk of frailty because insulin resistance produces a negative impact on skeletal muscle function and on vascular function.<sup>22</sup> Since higher visit-to-visit glycemia variability can aggravate insulin resistance, these patients are at higher risk of frailty. High visit-to-visit blood pressure variability was demonstrated to be associated with an increased incident rate of frailty in older adults from a large cohort study.<sup>33</sup>

The clinical frailty scale (CFS) is a promising frailty screening tool that has been proven to be associated with clinical outcomes in different diseases as we mentioned above. In the prospective, multi-center, longitudinal study, CFS was confirmed as a good independent negative prognostic factor of long-term mortality in the patients who were hospitalized in the intensive care unit.<sup>34</sup> In another study by Bradley NA et al, CFS showed good prognostic value in patients with chronic limb-threatening ischemia.<sup>35</sup> Han SJ et al evaluated the association between CFS and clinical outcomes and CFS was demonstrated to be useful in screening high-risk patients.<sup>36</sup> In a meta-analysis that enrolled 17 studies (n = 45,022), CFS was confirmed as an accurate and reliable tool for predicting short-term mortality in emergency patients.<sup>25</sup> The usefulness of CFS in T2DM patients was also evaluated in a study that enrolled 400 patients (35.3% of them were T2DM patients), the study showed that frailty was more common in patients with diabetes and patients with diabetes, the CFS was higher, and with worse clinical outcomes.<sup>37</sup>

Our study, so far as we know, for the first time revealed that higher CFS was associated with higher visit-to-visit glycemia variability in T2DM patients. This result highlights the importance of stable glycemic control could be beneficial to reduce the potential risk of frailty.

Our study has some limitations. First, this is a retrospective study, even if we performed PSM to limit the influence of other parameters, potential biases still might exist, so prospective studies are needed to confirm our findings. Second, our study is a single-center study with relatively limited participants, so multi-center studies with more enrolled patients are required. Third, we applied CFS to evaluate the frailty status and the predictive value of other frailty scoring systems still needs to be verified. Fourth, the visit-to-visit glycemic variability in our study was evaluated by HVS, which was relatively simple and easy compared with other variability parameters including coefficient of variation, standard

deviation, corrected variability independent of the mean (cVIM), etc. cVIM), etc. So the predictive value of these parameters still needs to be verified.

In conclusion, our study reveals that high CFS is associated with high visit-to-visit HbA1C variability and CFS has good clinical value in predicting HVS. Future studies are still needed to confirm our findings.

## Data Sharing Statement

The authors will supply the relevant data in response to reasonable requests.

## Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Beijing Tongren Hospital, Capital Medical University (TR-LCHL-23-105), which met the requirements of the Helsinki Declaration for clinical research. Informed consent was obtained from the patients or their family members who participated in our study.

## Consent for Publication

All authors agreed to publish this study in our journal.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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