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Association between hemoglobin glycation index and myocardial infarction in critically ill patients with diabetes mellitus: a retrospective study based on MIMIC-IV

Dongmei Gao[1] and Aiping Wang[2*]

Abstract

Background The hemoglobin glycation index (HGI), which quantifies the difference between observed and predicted hemoglobin A1c (HbA1c) levels, has been linked to adverse outcomes. However, its relationship with myocardial infarction (MI) in patients with diabetes mellitus (DM) remains unexplored. This study aimed to investigate the association between HGI and MI incidence in critically ill patients with diabetes mellitus (DM) using data from the MIMIC-IV database.

Methods Linear regression analysis of HbA1c and fasting blood glucose levels was conducted to calculate HGI. Subsequently, differences in MI incidence across HGI quartiles were assessed using the Kaplan-Meier survival analysis, with the log-rank test applied. Cox proportional hazards models and restricted cubic spline (RCS) analyses were conducted to estimate hazard ratios (HRs) for MI risk across HGI quartiles, with Q1 as the reference.

Results A total of 8,055 DM patients with an initial ICU admission exceeding 24 h were included, with 21.5% of them presenting MI. Compared to HGI Q1 (-3.81, -1.236), the risk of MI increased by 1.26 times in Q2 (HR: 1.26, 95% confidence interval [CI]: 1.10–1.45), 1.48 times in Q3 (HR: 1.48, 95% CI: 1.29–1.69), and 1.39 times in Q4 (HR: 1.39, 95% CI: 1.21–1.60). RCS analysis showed a nonlinear positive association between HGI and outcome events that remained consistent across different subgroups as the stratified analysis suggested.

Conclusion A significant correlation was revealed between HGI and the risk of MI in patients with DM, especially among those with elevated HGI levels, suggesting that HGI may serve as a potential biomarker for assessing MI risk in this population.

Keywords Diabetes mellitus, Myocardial infarction, Hemoglobin glycated index, MIMIC-IV

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Introduction

Diabetes mellitus (DM) remains a chronic global health concern that increases the risk of various complications, notably cardiovascular diseases (CVDs), nephropathy, retinopathy, and neurological damage. These complications not only adversely impact patients' quality of life but also impose tremendous burdens on global socioeconomic structures. Therefore, it is of critical significance to prevent the onset of DM and effectively manage its progression [1].

Despite advances in the management of DM, coronary artery disease (CAD) remains a major concern to be addressed. In CAD, the accumulation of lipid plaques within the coronary arteries progressively restricts blood flow to the heart, potentially causing severe cardiovascular events. While significant improvements have been made in the early diagnosis and treatment of CAD, the morbidity and mortality of this disease remain alarmingly elevated, particularly among patients who are at a higher risk of CAD, accompanied by DM [2].

As a serious and often fatal complication of CAD, myocardial infarction (MI) typically arises from the rupture of arterial plaque, resulting in vascular obstruction and cessation of blood supply to the heart. If not promptly treated, MI can cause extensive cardiac damage or even sudden death [3], contributing to cardiovascular mortality, particularly in individuals with DM. In DM, chronic hyperglycemia accelerates vascular wall damage, promoting atherosclerosis and plaque formation, thereby elevating the risk of MI [4].

Hemoglobin A1c (HbA1c), the gold standard for long-term glycemic control, reflects average blood glucose over 2–3 months but exhibits variability from factors like erythrocyte lifespan and glycation heterogeneity [5, 6]. Conversely, fasting blood glucose (FBG) captures acute glycemia but overlooks chronic fluctuations and tissue damage [7]. While these two metrics are complementary, they may not adequately stratify risks in discordant cases. The hemoglobin glycation index (HGI)—calculated as the residual between observed and FBG-predicted HbA1c—quantifies interindividual glycation variability [8, 9]. High HGI signifies disproportionately elevated HbA1c relative to FBG, indicating susceptibility to vascular complications despite comparable FBG [10]. HGI has distinct advantages over FBG or HbA1c alone in predicting the risk of DM complications. HbA1c may not fully capture individual variations in response to glycemic management, while HGI, by quantifying the discrepancy between HbA1c and FBG, facilities the identification of individual differences in glucose metabolism among patients with similar FBG levels [7]. This provides an approach for more comprehensively understanding the glucose dynamics, especially in patients whose HbA1c and FBG levels are discordant, thereby identifying individuals at a higher risk of metabolic abnormalities [5].

Research has demonstrated that HGI is a strong predictor of all-cause mortality and various complications of DM, including CVD, and microvascular complications [8, 9]. Given that only considering the FBG level may underestimate the long-term impact of hyperglycemia on tissue damage, and relying solely on HbA1c might overlook the short-term risks from acute glucose fluctuations [10], HGI, as a complementary marker to FBG and HbA1c, has been considered to offer more accurate identification of high-risk diabetic patients, enabling earlier monitoring and intervention. This study aimed to calculate HGI based on data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database through a linear regression model and analyze its correlation with MI in critically ill patients with DM.

Materials and methods

Study data

Data for this study were obtained from the MIMIC-IV 3.0 database, a publicly accessible database of clinical data in emergency and critical care medicine. The MIMIC database includes detailed patient information obtained from the critical care system at Beth Israel Deaconess Medical Center, covering the period from 2008 to 2022. It encompasses comprehensive records including demographics, surgical information, various clinical scores, laboratory indicators, medication records, vital signs, and survival prognosis [11]. As an anonymous public database, MIMIC is compliant with institutional review board protocols, with all personal information de-identified.

Study population

Cohort selection was based on the International Classification of Diseases (ICD)-9 and – 10 codes. Patients meeting the following criteria were excluded (Fig. 1): (1) Age below 18 years; (2) Non-first-time ICU admissions; (3) ICU stay of less than 24 h; or (4) With missing data on HbA1c or FBG.

Data extraction

Data were extracted using SQL with PostgreSQL (version 16.3.2). The potential confounding variables included were as follows: (1) Baseline demographics: age, gender, marital status, and race; (2) Comorbidities: chronic obstructive pulmonary disease (COPD), hypertension, congestive heart failure (CHF), severe liver disease, and chronic kidney disease (CKD); (3) Laboratory parameters: partial thromboplastin time (PTT), hemoglobin (HGB), white blood cells (WBC), platelets (PLT), red blood cells (RBC), prothrombin time (PT), systolic blood pressure (SBP), heart rate, mean arterial pressure (MAP),

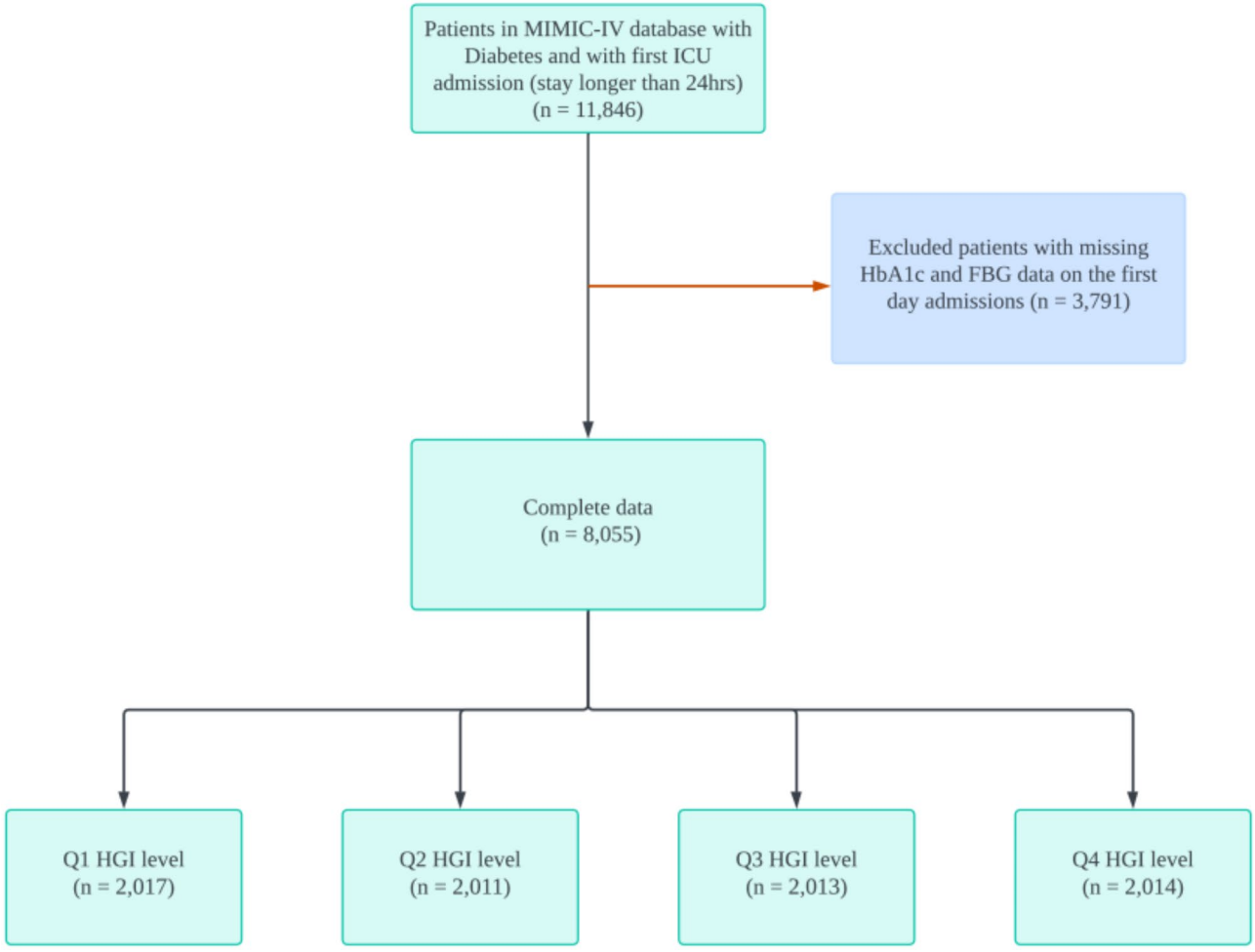

Fig. 1 Flow chart of the patient selection process in this study. A total of 11,846 patients with DM admitted to the ICU were initially screened. Among them, 3,791 (32.0%) were excluded due to missing HbA1c or FBG data on their first day of admission. The final analysis included 8,055 patients, who were subsequently categorized into HGI quartiles

international normalized ratio (INR), oxygen saturation (SpO2), diastolic blood pressure (DBP), mean corpuscular volume (MCV), hematocrit, mean corpuscular hemoglobin content (MCH), temperature, lymphocytes, neutrophils, and Estimated Glomerular Filtration Rate (eGFR); (4) Severity scores: Sepsis-Organ Failure Assessment Score (SOFA), Acute Physiology Score III (APSIII), Systemic Inflammatory Response Syndrome (SIRS), and Simplified Acute Physiology Score II (SAPSII).

The eGFR was calculated using the following formula: (*1 for males)

eGFR (ml/ (min*1.73m2)) = 186 x (Scr)^-1.154 x (age)^-0.203 × (0.742 for females)

Definition of exposure variables and outcome events

A linear regression model was developed to assess the relationship between FBG and HbA1c. The predicted HbA1c was calculated using the equation: Predicted HbA1c = 0.0054*FBG + 6.7. The relationship between HbA1c and FBG is displayed in Fig. 2. The primary outcome was the incidence of MI, while the secondary outcome was defined as in-hospital mortality after admission.

Statistical analyses

The enrolled participants were divided into four groups based on HGI quartiles: group Q1 ($n = 2017$, HGI ≤ -1.236), group Q2 ($n = 2011$, $-1.236 < \text{HGI} \leq -0.533$), group Q3 ($n = 2013$, $-0.533 < \text{HGI} \leq 0.687$), and group Q4 ($n = 2014$, $\text{HGI} > 0.687$). Categorical variables were expressed as percentages, with intergroup comparisons conducted using the chi-square test. Continuous variables were summarized as quartiles following normality testing, and the nonparametric rank-sum test was used for intergroup comparisons. Hazard ratios (HR) for HGI as a risk factor for outcome events were assessed using a Cox proportional hazards model, with group Q1 as the reference group. Potential confounding variables were

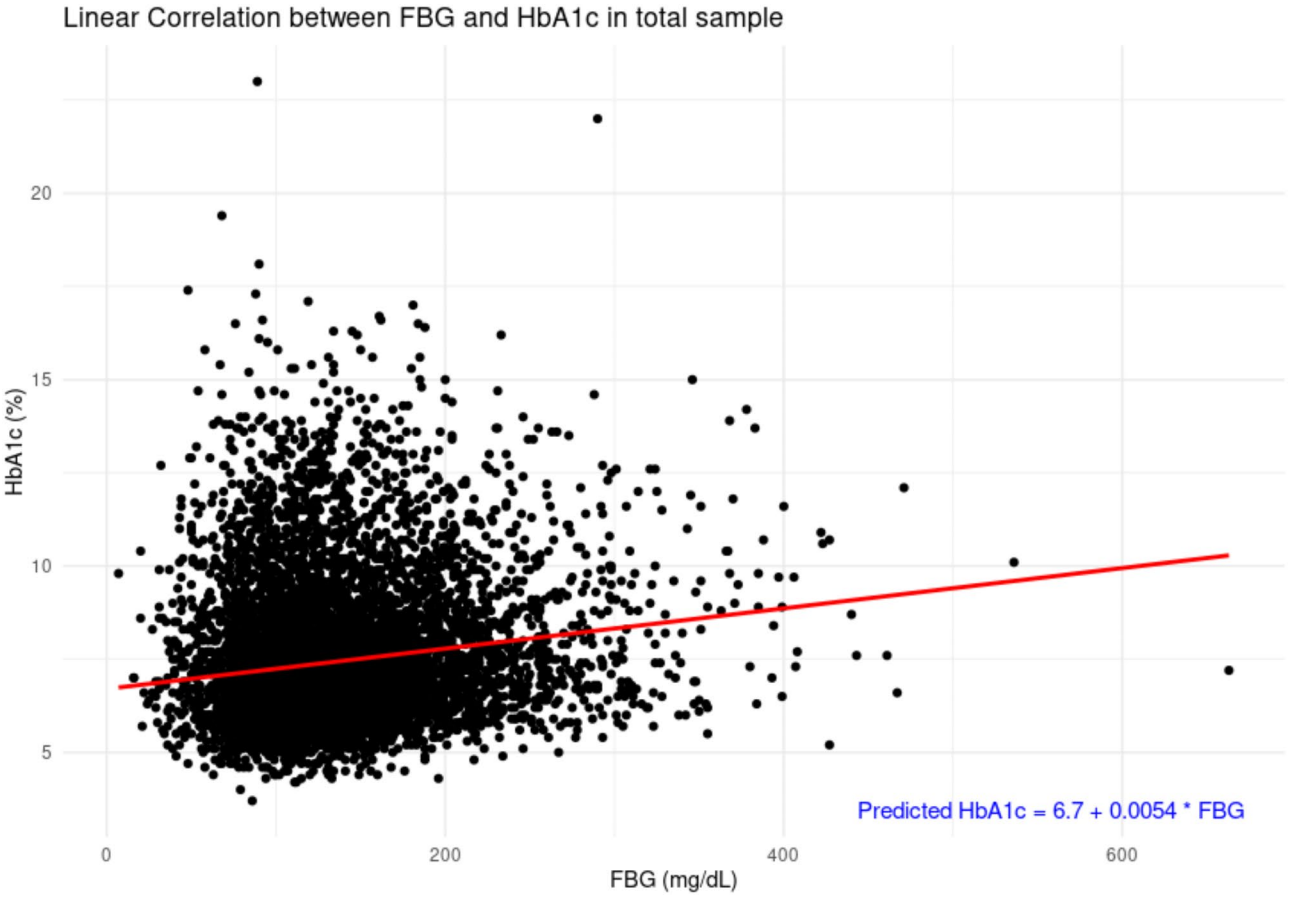

Fig. 2 Linear correlation between FBG and HbA1c, with and the equation for predicted HbA1c: Predicted HbA1c = 0.0054*FBG + 6.7

included in a multivariate Cox regression model and tested for trends. Differences between groups were analyzed using Kaplan-Meier (KM) survival analysis based on the HGI quartiles, supplemented by log-rank tests. Restricted cubic spline (RCS) curves were employed to elucidate the association between HGI and the incidence of MI.

Results

HGI-based comparison of patients' baseline information

The baseline characteristics of the 8,055 eligible patients, categorized into four HGI groups (Q1, Q2, Q3, and Q4), are concluded in Table 1. We observed no statistically significant differences in SpO2, lymphocytes, neutrophils, APSIII, or SIRS scores among the four groups. Age distribution varied significantly across the four HGI groups, with the highest proportion of elderly patients in Q2 (68.27%) and the lowest in Q4 (40.42%).

Patients in Q4 exhibited significantly higher hemoglobin levels (10.800 g/dL) and erythrocyte counts (3.72×10^{12}/L) compared to those in other quartiles. In contrast, patients in Q3 and Q4 were found to show significantly higher leukocyte levels and a higher prevalence of CKD. CHF was most prevalent in patients in Q3 (35.37%), whereas severe liver disease was more common in patients in Q1 and Q2.

KM analysis of the cumulative risk of MI and in-hospital mortality

As shown in Fig. 3, KM survival analysis revealed significant differences in the cumulative incidence of MI and in-hospital mortality across HGI quartiles. The Q1 group exhibited the lowest incidence of MI, with a log-rank p-value of < 0.0001 (Fig. 3A). In contrast, the Q4 group showed a significantly higher risk of in-hospital mortality compared to other quartiles (log-rank $p = 0.00056$; Fig. 3B). To clarify potential discrepancies in the visual interpretation of Fig. 3B, detailed event numbers and percentages are provided in Supplementary Table 1. Notably, while the Q4 survival curve appears higher (indicating lower mortality) during the early follow-up period, it sharply declines beyond day 60, ultimately demonstrating the poorest survival outcome. This temporal pattern aligns with the statistical significance of the log-rank test.

Correlation analysis between HGI and the incidence of MI

To assess the association between HGI and the incidence of MI, several Cox proportional hazard models were

Table 1 Comparison of baseline information of the patients according to the HGI

	level	Overall	Q1	Q2	Q3	Q4	*P*-value
Number		8055	2017	2011	2013	2014	
Age (%)	> 65	4676 (58.05)	1224 (60.68)	1373 (68.27)	1265 (62.84)	814 (40.42)	< 0.0001
	≤ 65	3379 (41.95)	793 (39.32)	638 (31.73)	748 (37.16)	1200 (59.58)	
Gender (%)	F	3312 (41.12)	851 (42.19)	854 (42.47)	774 (38.45)	833 (41.36)	0.0378
	M	4743 (58.88)	1166 (57.81)	1157 (57.53)	1239 (61.55)	1181 (58.64)	
Race (%)	Black	1309 (16.25)	297 (14.72)	316 (15.71)	290 (14.41)	406 (20.16)	< 0.0001
	Others	1732 (21.50)	390 (19.34)	412 (20.49)	463 (23.00)	467 (23.19)	
	White	5014 (62.25)	1330 (65.94)	1283 (63.80)	1260 (62.59)	1141 (56.65)	
Marital status (%)	Divorced	621 (7.71)	141 (6.99)	146 (7.26)	155 (7.70)	179 (8.89)	< 0.0001
	Married	3858 (47.90)	927 (45.96)	1021 (50.77)	1029 (51.12)	881 (43.74)	
	Others	377 (4.68)	87 (4.31)	91 (4.53)	94 (4.67)	105 (5.21)	
	Single	2198 (27.29)	582 (28.85)	464 (23.07)	472 (23.45)	680 (33.76)	
	Widowed	1001 (12.43)	280 (13.88)	289 (14.37)	263 (13.07)	169 (8.39)	
INR (median [IQR])		1.200 [1.100, 1.400]	1.200 [1.100, 1.500]	1.200 [1.100, 1.400]	1.200 [1.100, 1.400]	1.200 [1.100, 1.300]	< 0.0001
PT (median [IQR])		13.200 [11.900, 15.500]	13.400 [12.000, 16.200]	13.300 [12.100, 15.800]	13.200 [11.900, 15.300]	12.900 [11.650, 14.800]	< 0.0001
PTT (median [IQR])		31.000 [27.400, 39.900]	31.800 [27.900, 41.600]	31.200 [27.600, 40.700]	30.800 [27.075, 38.425]	30.300 [26.800, 38.300]	< 0.0001
Heart rate (median [IQR])		83.250 [74.381, 93.375]	83.014 [73.383, 93.885]	82.370 [73.832, 92.464]	82.509 [74.571, 91.945]	85.094 [75.850, 95.236]	< 0.0001
SBP (median [IQR])		117.500 [108.200, 130.401]	117.286 [107.355, 130.208]	117.027 [107.920, 129.687]	117.465 [108.610, 130.027]	118.319 [109.542, 132.028]	0.001
DBP (median [IQR])		60.389 [54.219, 68.560]	60.364 [54.175, 68.243]	59.481 [53.553, 67.370]	59.213 [53.423, 67.343]	62.929 [56.243, 70.625]	< 0.0001
MBP (median [IQR])		76.320 [70.577, 84.160]	76.350 [70.319, 84.520]	75.667 [70.000, 83.220]	75.310 [70.152, 83.258]	77.965 [71.896, 86.000]	< 0.0001
SPO2 (median [IQR])		97.259 [95.913, 98.500]	97.200 [95.800, 98.439]	97.261 [95.880, 98.437]	97.180 [95.941, 98.529]	97.387 [96.039, 98.577]	0.0512
Hemoglobin (median [IQR])		10.600 [9.100, 12.300]	10.600 [8.900, 12.200]	10.600 [9.100, 12.100]	10.500 [9.100, 12.100]	10.800 [9.100, 12.600]	0.0058
Hematocrit (median [IQR])		32.100 [27.900, 37.000]	31.900 [27.500, 37.000]	32.000 [27.900, 36.800]	32.050 [27.925, 36.600]	32.700 [28.100, 37.675]	0.0014
MCV (median [IQR])		90.000 [86.000, 94.000]	91.000 [87.000, 96.000]	90.000 [86.000, 94.000]	90.000 [86.000, 94.000]	89.000 [85.000, 93.000]	< 0.0001
MCH (median [IQR])		29.700 [28.000, 31.100]	30.100 [28.500, 31.500]	29.700 [28.000, 31.100]	29.500 [28.000, 30.900]	29.300 [27.700, 30.700]	< 0.0001
Temperature (median [IQR])		36.803 [36.590, 37.057]	36.803 [36.591, 37.057]	36.797 [36.586, 37.042]	36.790 [36.584, 37.039]	36.826 [36.602, 37.082]	0.0175
RBC (median [IQR])		3.620 [3.110, 4.200]	3.540 [3.020, 4.130]	3.590 [3.100, 4.170]	3.620 [3.130, 4.162]	3.720 [3.170, 4.320]	< 0.0001
WBC (median [IQR])		8.600 [6.500, 11.700]	8.300 [6.100, 11.400]	8.600 [6.500, 11.675]	8.900 [6.800, 11.800]	8.800 [6.600, 11.800]	< 0.0001
eGFR (median [IQR])		29.729 [0.000, 58.091]	23.641 [0.000, 58.050]	28.422 [0.000, 56.846]	34.995 [0.000, 58.771]	31.048 [0.000, 59.050]	0.0142
Lymphocytes (median [IQR])		19.300 [12.100, 27.200]	18.900 [11.700, 26.900]	19.600 [12.700, 27.500]	19.500 [12.600, 27.000]	19.000 [11.500, 27.300]	0.1513
Neutrophils (median [IQR])		71.400 [62.500, 80.000]	71.200 [62.000, 79.900]	71.000 [62.600, 79.800]	71.000 [62.800, 79.600]	72.400 [62.600, 80.800]	0.1591
APSIII (median [IQR])		42.000 [31.000, 55.000]	42.000 [31.000, 56.000]	41.000 [31.000, 55.000]	41.000 [31.000, 54.000]	42.000 [32.000, 54.000]	0.3572
SAPSII (median [IQR])		35.000 [28.000, 44.000]	36.000 [29.000, 45.000]	36.000 [30.000, 45.000]	35.000 [28.000, 44.000]	33.000 [25.000, 42.000]	< 0.0001
SIRS (median [IQR])		3.000 [2.000, 3.000]	3.000 [2.000, 3.000]	3.000 [2.000, 3.000]	3.000 [2.000, 3.000]	3.000 [2.000, 3.000]	0.1052

Table 1 (continued)

	level	Overall	Q1	Q2	Q3	Q4	*P*-value
SOFA (median [IQR])		4.000 [2.000, 6.000]	5.000 [2.000, 7.000]	4.000 [2.000, 6.000]	4.000 [2.000, 6.000]	4.000 [2.000, 6.000]	< 0.0001
Insulin (%)	No	169 (2.10)	109 (5.40)	49 (2.44)	8 (0.40)	3 (0.15)	< 0.0001
	Yes	7886 (97.90)	1908 (94.60)	1962 (97.56)	2005 (99.60)	2011 (99.85)	
Myocardial infarction	No	6327 (78.55)	1645 (81.56)	1583 (78.22)	1540 (76.50)	1559 (77.41)	0.0006
	Yes	1728 (21.45)	372 (18.44)	428 (21.28)	473 (23.50)	455 (22.59)	
CKD (%)	No	6177 (76.69)	1532 (75.95)	1596 (79.36)	1566 (77.79)	1483 (73.63)	0.0001
	Yes	1878 (23.31)	485 (24.05)	415 (20.64)	447 (22.21)	531 (26.37)	
CHF (%)	No	5467 (67.87)	1390 (68.91)	1345 (66.88)	1301 (64.63)	1431 (71.05)	0.0001
	Yes	2588 (32.13)	627 (31.09)	666 (33.12)	712 (35.37)	583 (28.95)	
COPD (%)	No	7139 (88.63)	1740 (86.27)	1775 (88.26)	1796 (89.22)	1828 (90.76)	0.0001
	Yes	916 (11.37)	277 (13.73)	236 (11.74)	217 (10.78)	186 (9.24)	
Severe liver disease (%)	No	7782 (96.61)	1899 (94.15)	1964 (97.66)	1956 (97.17)	1963 (97.47)	< 0.0001
	Yes	273 (3.39)	118 (5.85)	47 (2.34)	57 (2.83)	51 (2.53)	
Hypertension (%)	No	2300 (28.55)	574 (28.46)	527 (26.21)	552 (27.42)	647 (32.13)	0.0002
	Yes	5755 (71.45)	1443 (71.54)	1484 (73.79)	1461 (72.58)	1367 (67.87)	

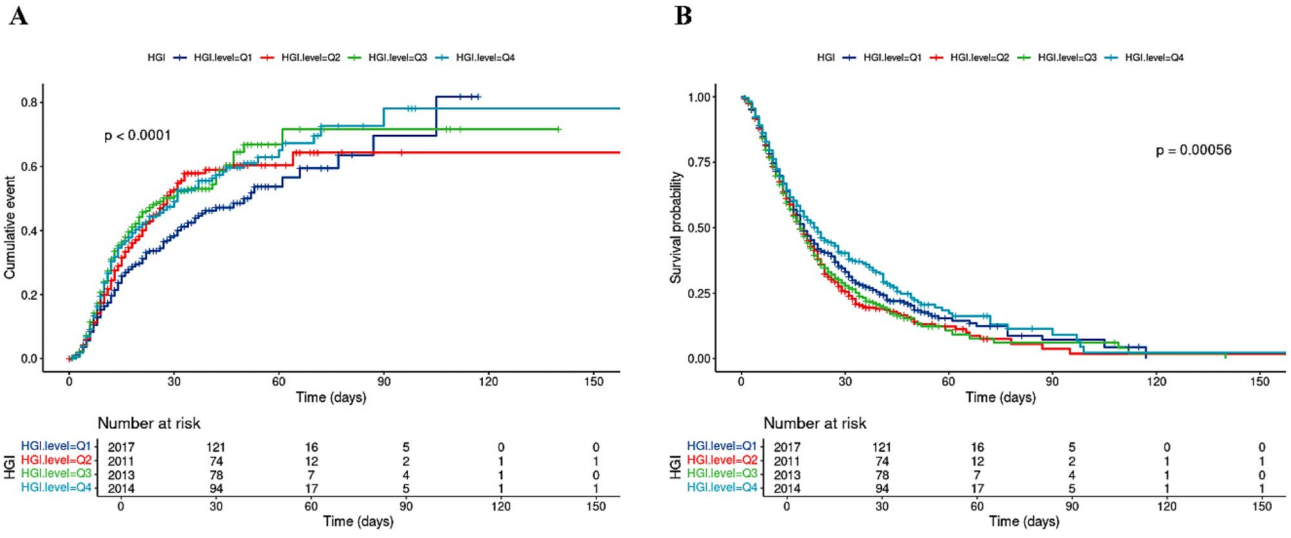

Fig. 3 KM survival curves comparing **A**: cumulative incidence of MI and **B**: in-hospital mortality among different HGI groups. The transiently higher survival probability in the Q4 group during early follow-up may reflect short-term therapeutic interventions or enrollment bias. However, the long-term risk diverges markedly, with Q4 exhibiting the lowest 150-day survival rate (45% vs. 68% in Q2 and 62% in Q3)

constructed, with Q1 as the reference (Table 2). In the unadjusted Model 1, the incidence of MI was significantly elevated in groups Q2, Q3, and Q4, with HR of 1.26 (95% confidence interval [CI]: 1.10–1.45, $p = 0.001$) for Q2, 1.48 (95% CI: 1.29–1.69, $p < 0.001$) for Q3, and 1.39 (95% CI: 1.21–1.60, $p < 0.001$) for Q4, suggesting a significant association between higher HGI levels and increased MI risk (HR > 1, $p < 0.001$). In Model 2, which adjusted for demographics, the Q4 group exhibited the highest MI incidence (HR = 1.52, 95% CI: 1.32–1.75, $p < 0.001$), while the HRs in Q2 and Q3 were slightly reduced. After further adjustment for additional confounding variables in Model 3, the association remained significant in groups Q3 and Q4, with HRs of 1.30 (95% CI: 1.06–1.58, $p = 0.010$) for Q3 and 1.46 (95% CI: 1.20–1.78, $p < 0.001$) for Q4. However, the risk of MI in group Q2 was no longer statistically significant.

To further illustrate the relationship between HGI and the incidence of MI, the RCS method (Fig. 4) was employed to account for nonlinear trends. With the solid line representing the estimated HR of HGI and the shaded area denoting the 95% CI, a statistically significant association between HGI and MI incidence characterized by a nonlinear relationship was observed. Notably,

Table 2 Association between HGI and the incidence of MI in patients with DM

HGI levels	Model 1		Model 2		Model 3	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
Q1	Ref.		Ref.		Ref.	
Q2	1.26 (1.10–1.45)	0.001	1.24 (1.08–1.42)	0.003	1.20 (0.98–1.46)	0.074
Q3	1.48 (1.29–1.69)	< 0.001	1.47 (1.29–1.69)	< 0.001	1.30 (1.06–1.58)	0.010
Q4	1.39 (1.21–1.60)	< 0.001	1.52 (1.32–1.75)	< 0.001	1.46 (1.20–1.78)	< 0.001

Model 1: unadjusted model; Model 2: adjusted by age, gender, race, and marital status; Model 3: adjusted by all the factors included in this research

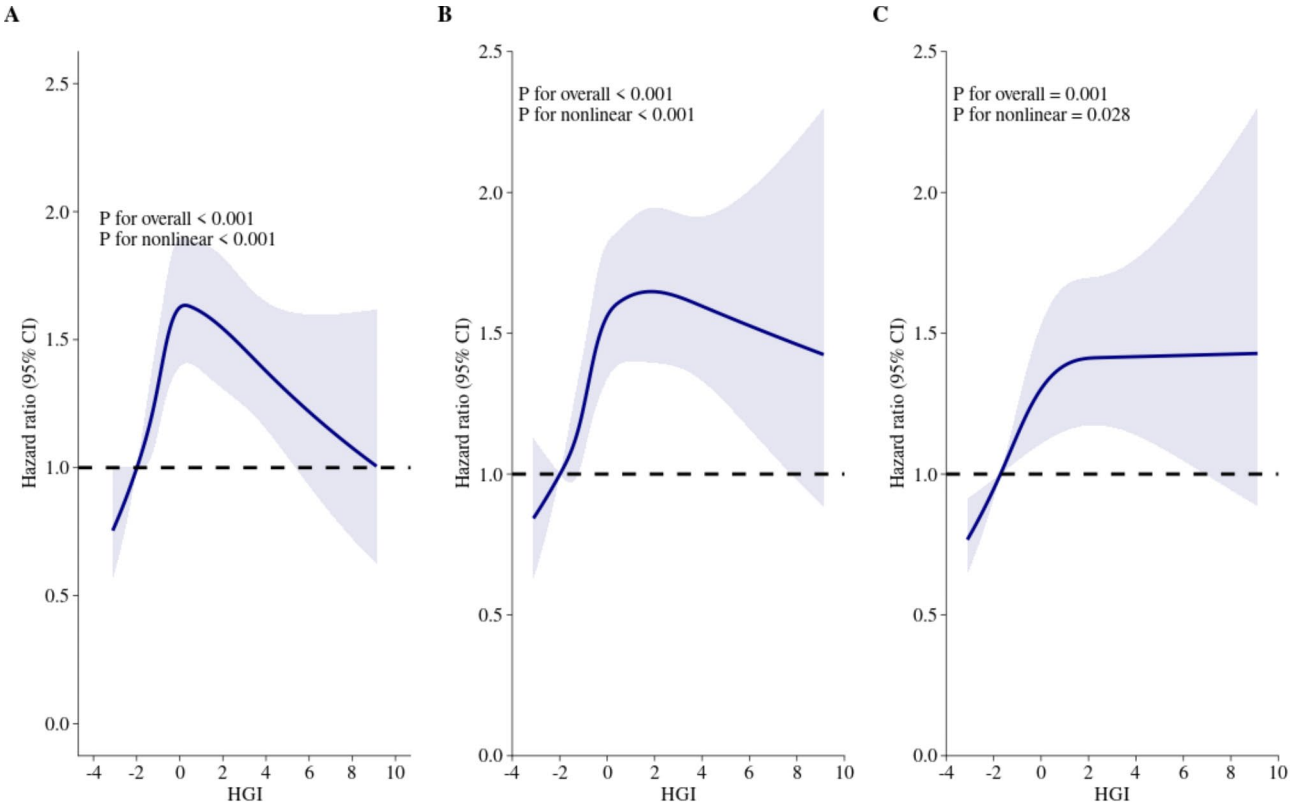

Fig. 4 RCS curve displaying the HRs of HGI in different Cox proportional hazard models. **A**: RCS curve for model 1, **B**: RCS curve for model 2, and **C**: RCS curve for model 3

the risk of MI increased significantly with the elevation of HGI values, especially when HGI was positive, indicating a positive association.

Subgroup analysis

We assessed the prognosis of patients by performing subgroup analyses based on comorbidities such as hypertension, CHF, CKD, and COPD. As shown in Fig. 5, in patients with DM aged over 65 years with conditions such as CHF, the risk of MI were revealed to be strongly correlated with HGI, suggesting that higher HGI values within specific subgroups are associated with an elevated incidence of MI. Subgroup analyses demonstrated that higher HGI quartiles (Q4) were associated with elevated MI risk (HR = 1.44, 95% CI 1.25–1.66) under the simplified adjustment model. Differences in HRs compared to Model 3 in Table 2, arise from the exclusion of laboratory parameters in the forest plot analysis.

Discussion

DM remains a major health concern worldwide that needs to be addressed, and it has been confirmed to be in close association with CVD. Both diabetes and prediabetes are usually associated with hyperglycemia and insulin resistance, leading to an increase in reactive oxygen species (ROS) and activation of intracellular signaling pathways. This process contributes to a pro-thrombotic state and promotes increased inflammatory mediators, accelerating the progression of atherosclerosis and ultimately macrovascular disease. Consequently, patients with diabetes or prediabetes are more susceptible to serious cardiovascular events [12, 13]. MI remains one of the leading causes of mortality among patients with DM.

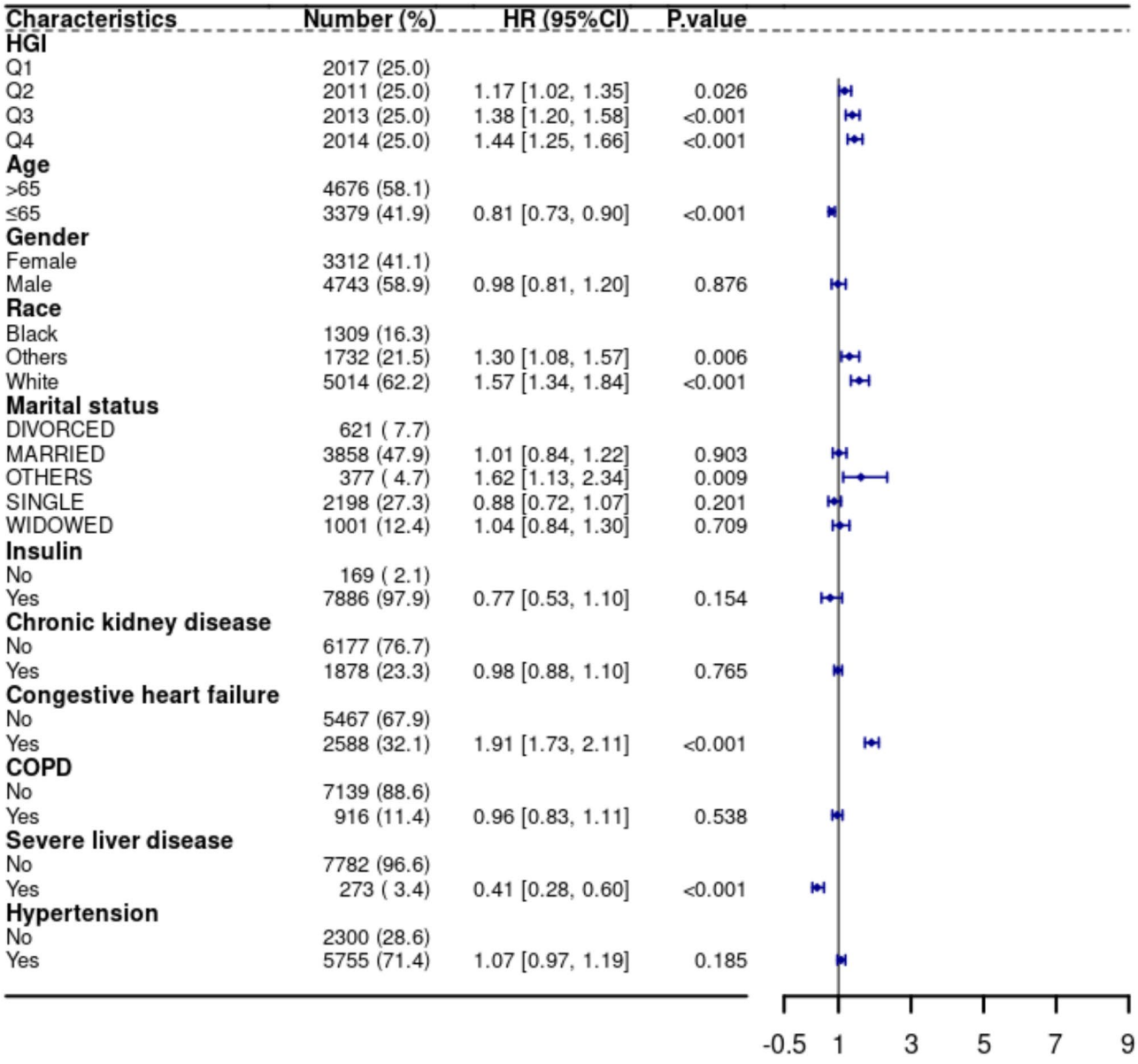

Fig. 5 Subgroup analysis of HRs for MI across different characteristics. Higher HGI quartiles (Q2-Q4) were associated with significantly elevated MI risk (Q4 HR = 1.44, 95% CI 1.25–1.66, $p < 0.001$)

Although advancements in thrombolytic therapy and pharmacological treatments (e.g., aspirin, β-blockers, and angiotensin-converting enzyme inhibitors) have shown to reduce the mortality among MI patients, poor metabolic control continues to pose a major challenge in this population [14, 15].

Large-scale studies have demonstrated that optimizing glycemic control in DM patients without a prior history of cardiac disease resulted in a nonnegligible reduction in the incidence of heart disease and MI [16]. In addition, antihypertensive treatment has been shown to be effective in preventing cardiovascular events in patients with DM. However, whether the treatment of hyperlipidemia can further reduce the risk of MI remains a subject of ongoing investigation [17, 18]. Under this circumstance, this study investigated the relationship between HGI and the incidence of MI in patients with DM precisely using the MIMIC-IV database. Our experimental results revealed a significant positive association between them, contributing to a deeper understanding of MI risk in this population and providing a scientific basis for the development of targeted clinical interventions.

HGI quantifies interindividual disparities in HbA1c levels relative to FBG, capturing inherent variability in glucose metabolism. Notably, elevated HGI reflects prolonged hyperglycemic exposure, even in individuals with

"normal" HbA1c levels, through mechanisms involving chronic glycation. Excessive glucose flux promotes non-enzymatic glycation of proteins and lipids, leading to the generation of advanced glycation end products (AGEs). These AGEs accumulate in vascular tissues, bind to receptors (RAGE) to activate inflammatory cascades (e.g., NF-κB), amplify oxidative stress, and induce endothelial dysfunction—key drivers of atherosclerotic plaque formation and instability [19–22]. This mechanistic link explains why higher HGI correlated with increased MI risk in our cohort. Prior studies have linked elevated HGI to microvascular complications (e.g., retinopathy, nephropathy) [21], but its role in macrovascular disease remains contentious [17, 23]. Our results bridge this gap, demonstrating that HGI captures metabolic derangements beyond HbA1c or FBG alone, particularly chronic glycemic variability linked to AGE-mediated vascular injury. Traditional glycemic indices, such as HbA1c and FBG, possess unique advantages but are limited in their ability to monitor long-term glycemic control comprehensively. HbA1c can be affected by factors such as red blood cell longevity and anemia, while FBG mainly reflects short-term glycemic fluctuations [19, 20]. HGI addresses these gaps by integrating both measures to estimate an individual's propensity for glycation. This is especially critical given that glycemic variability—even within normoglycemic ranges—induces ROS bursts, endothelial damage, and plaque vulnerability [24]. These metabolic differences are crucial for predicting cardiovascular complications (e.g., MI), as chronic blood glucose fluctuations contribute to the accumulation of AGEs, which have been shown to be strongly associated with atherosclerosis, inflammatory responses, and endothelial dysfunction [22]. Thus, increased HGI suggests higher glycosylation levels in individuals with chronic glycemic exposure, potentially elucidating mechanisms behind the increased risk of MI.

This study further confirms the significant association between HGI and the risk of MI in patients with DM. Higher HGI levels corresponded with an increased risk of MI, which is in line with the findings of prior studies on the role of HGI in reflecting long-term metabolic disorders [24]. Notably, patients within the Q1 group, despite having the lowest HGI, also exhibited MI risk, likely related to elevated FBG levels, a known cardiovascular risk factor [25, 26]. This suggests that relying on HGI alone to assess MI risk may have limitations [27]. Our findings indicate that in patients with DM, neither HbA1c nor HGI alone adequately captures the impact of metabolic disorders on cardiovascular health. Despite the difference in HGI levels, the observation that both the Q1 and Q4 groups exhibited increased MI risk highlights the necessity of incorporating additional metabolic markers, such as FBG and insulin resistance, into cardiovascular risk assessments [28].

In addition, this study underscores the important role of traditional cardiovascular risk factors in patients with DM. Advanced age and a history of CHF were revealed to be associated with a higher risk of MI, which was consistent with existing literature [29]. Furthermore, White patients exhibited a significantly higher risk of MI than other racial groups, possibly reflecting disparities in genetics, lifestyle, or access to healthcare resources [30]. Meanwhile, patients with chronic liver disease demonstrated a lower risk of MI, possibly due to liver dysfunction affecting glucose and lipid metabolism, thereby slowing the progression of atherosclerosis [31].

In critically ill patients, short-term metabolic disturbances (e.g., stress hyperglycemia) are strongly associated with adverse clinical outcomes and can exacerbate the severity of CAD, leading to endothelial dysfunction and microvascular occlusion [32, 33]. HGI has the advantage of capturing metabolic heterogeneity that is not reflected by HbA1c and FBG, which is particularly useful for identifying patients with normal HbA1c levels who nonetheless face elevated cardiovascular risks [24]. Future studies should integrate HGI with other metabolic markers, such as insulin resistance and inflammatory markers, to construct a more comprehensive cardiovascular risk assessment model to optimize personalized management of DM [34].

Our findings highlight HGI's potential in identifying "discordant" patients with normal HbA1c levels but high propensity for glycation, who may benefit from earlier interventions such as statin or GLP-1RA therapy to mitigate AGE-related vascular injury. Conversely, patients with low HGI but elevated FBG may benefit from stricter glucose monitoring. The observed impact of traditional risk factors, including age, CHF, and race, emphasizes the need for multifactorial management, while the lower MI risk in chronic liver disease patients warrants further investigation [31]. This study's strengths include using the MIMIC-IV database and adjusting for confounders, focusing on critically ill patients with DM. However, potential residual confounding and demographic differences across HGI quartiles may limit causal inferences. Future studies should validate HGI's prognostic value and investigate its integration with omics-derived biomarkers [34]. Given the complexity of ICU patients, large-scale prospective studies are necessary to fully elucidate HGI's role in predicting poor prognosis. A more comprehensive assessment combining HGI, FBG, and other metabolic markers may improve the prediction of cardiovascular risk and reduce the incidence of MI [35].

Limitations

Despite relevant clinical information obtained from the MIMIC-IV database, not all clinical diagnostic information was available, leaving the possibility of multiple unmeasured confounding factors. Second, the HGI calculated in this study may not be directly generalizable to other populations. Future research should incorporate more comprehensive data from various large-scale databases to develop a more generalized regression model for HGI estimation across different populations. Third, our study excluded 32.0% of the initial cohort due to missing HbA1c or FBG data. This high proportion of missing data raises concerns about potential selection bias, as excluded patients might differ systematically from those included (e.g., less frequent glucose monitoring in critically ill or unstable cases). Consequently, our findings may not fully represent the broader population with DM admitted to the ICU. Future studies should adopt advanced statistical techniques (e.g., multiple imputations) to address the challenges raised by missing data.

Conclusion

This study identified a nonlinear relationship between HGI and the incidence of MI in critically ill patients with DM based on patient data retrieved from the MIMIC-IV database. HGI was confirmed as an effective indicator of poor prognosis in critically ill patients with DM and a potential indicator of MI risk as well as short- and long-term mortality. Given its clinical significance, patients with abnormal HGI should be given extra attention upon their initial admission to the ICU.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04742-4.

Supplementary Material 1

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Author contributions
Dongmei Gao and Aiping Wang designed this study, Dongmei Gao analyzed the data and wrote the manuscript, Aiping Wang drew the images, and Aiping Wang checked manuscript.

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Data availability
The datasets analysed during the current study are available in the MIMIC-IV database (MIMIC-IV v3.0 (physionet.org)).

Declarations

Ethics approval and consent to participate
The MIMIC-IV database has obtained approval from the Institutional Review Boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. Informed consent from patients was not required as all protected private information was removed.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial number
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