Prognostic value of estimated glucose disposal rate in non-ST-segment elevation acute coronary syndrome cases administered percutaneous coronary intervention

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Research Article

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Abstract

Background: Estimated glucose disposal rate (eGDR) is highly associated with all-cause mortality in type 2 diabetes mellitus (T2DM) cases administered coronary artery bypass grafting (CABG). However, the predictive ability of eGDR for poor outcome in non-ST-segment elevation acute coronary syndrome (NSTE-ACS) cases diagnosed by percutaneous coronary intervention (PCI) remains unknown.

Methods: Totally 2308 NSTE-ACS patients administered PCI at Beijing Anzhen Hospital from January to December 2015 were enrolled in this study. Major adverse cardiac and cerebral events (MACCEs) were considered the primary endpoint. eGDR was calculated by waist circumference (WC) ($eGDR_{WC}$) or body mass index (BMI) ($eGDR_{BMI}$).

Results: The incidence of MACCEs was markedly higher in cases with low eGDR compared with the high eGDR group. Multivariable analysis showed hazard ratios (HRs) for $eGDR_{WC}$ and $eGDR_{BMI}$ of 1.152 (95% confidence interval [CI] 1.088-1.219; P<0.001) and 0.998 (95%CI 0.936-1.064; P=0.957). Addition of $eGDR_{WC}$ to a model that includes currently recognized cardiovascular risk factors markedly enhanced its predictive power (Harrell's C-index, $eGDR_{WC}$ versus Baseline model, 0.778 versus 0.768, P=0.003; continuous net reclassification improvement (continuous-NRI) 0.125, P<0.001; integrated discrimination improvement (IDI) 0.016, P<0.001).

Conclusion: Low eGDR independently predicts adverse outcome in NSTE-ACS cases administered PCI.

Introduction

Nowadays, cardiovascular disease (CVD) causes about one-third of deaths in the world, and its global morbidity and mortality, especially those of coronary artery disease (CAD), increase year by year; in addition, the aging population is exacerbating this trend [1, 2]. Considered a critical risk factor for CAD, type 2 diabetes mellitus (T2DM) also shows increasing incidence rate [1, 3]. As a significant mechanism underlying the occurrence and aggravation of T2DM, insulin resistance (IR) ultimately leads to vascular endothelial cell dysfunction and atherosclerosis by destroying nitric oxide synthesis, promoting increased reactive oxygen species (ROS) production and causing endothelial cell inflammation [4–6]. At the same time, IR can also cause lipid metabolism disorders [7]. These mechanisms will eventually cause atherosclerosis [8].

Regarding the measurement of IR, the hyperinsulinemic-euglycemic clamp, which is generally considered the best standard, is difficult to be widely applied clinically due to its high cost, time-consumption and invasive characteristics. In 2000, estimated glucose disposal rate (eGDR) was developed by researchers and verified by the hyperinsulinemic-euglycemic clamp to be able to evaluate insulin sensitivity in T1DM [9, 10]. eGDR was originally calculated from waist-to-hip ratio (WHR), hypertension and glycosylated hemoglobin (HbA1c). However, researchers also found that using waist circumference (WC) and body mass index (BMI) instead of WHR to calculate eGDR yielded the same results [9, 11]. The higher the eGDR, the higher the insulin sensitivity, and the lower the eGDR, the stronger the IR [12].

Many previous clinical trials revealed IR as a significant predictive factor of CVD onset and low survival [13–16]. Furthermore, researchers have found that IR has a tight association with prognosis in atherosclerotic cardiovascular disease (ASCVD) cases undergoing percutaneous coronary intervention (PCI) [17–20]. More importantly, in T2DM cases administered coronary artery bypass grafting (CABG), low eGDR is linked to enhanced risk of all-cause mortality in the long run, suggesting that eGDR may represent an important risk factor for T2DM with ischemic heart disease [21]. Nonetheless, eGDR's prognostic potential in CAD cases administered PCI remains uncertain. Therefore, this study aimed to evaluate eGDR for its prognostic potential in cases with non-ST-elevation acute coronary syndrome (NSTE-ACS) treated by PCI.

Materials And Methods

Study population

The current single-center, observational trial enrolled NSTE-ACS cases treated by PCI in Beijing Anzhen Hospital between Jan. and Dec. 2015. NSTE-ACS includes non-ST-segment elevation myocardial infarction [NSTEMI] and unstable angina [UA] [22]. Exclusion criteria were: (1) age < 18 years; (2) no information regarding baseline and follow-up data; (3) diagnosis of T1DM; (4) previous CABG, cardiogenic shock, acute decompensated heart failure, chronic infection or malignancies; (5) failed PCI, PCI complications, in-hospital death; (6) kidney function impairment with estimated glomerular filtration rate (eGFR) < 30 mL/(min×1.73 m^2) or renal replacement therapy, severely impaired liver function with alanine and/or aspartate transaminase levels ≥ 5 times the respective upper limits of normal. In the end, 2308 individuals were included (Fig. 1).

Data collection and definitions

Patient demographics and patient features were derived from the hospital's medical information record system. Definitions and diagnostic criteria for hypertension, dyslipidemia, stroke and peripheral arterial disease (PAD) are based on current guidelines [23–28]. The calculation formula for BMI was weight (kg)/[height (m)]^2. WC was the girth of the midpoint line between the lowest point of the rib and the upper border of the iliac crest. Blood samples were drawn in the morning of the surgery with the patient fasting for 8–12 hours. Hematological and biochemical parameters were examined by standard laboratory methods. Echocardiograms were evaluated by two ultrasound physicians. Procedures for coronary intervention followed currently available guidelines [29–31]. Data related to coronary lesion characteristics were assessed by at least two experienced cardiologists. Synergy between PCI with taxus and cardiac surgery (SYNTAX) scores were calculated by standard formula (http://www.syntaxscore.com).

In this study, eGDR (mg/kg/min) was assessed according to previously proposed formulae [9, 11, 32]: eGDR calculated by WC ($eGDR_{WC}$) = 21.16 − (0.09 * WC [cm]) − (3.41 * Hypertension) − (0.55 * HbA1c [%]); eGDR calculated by BMI ($eGDR_{BMI}$) = 19.02 − (0.22 * BMI [kg/m^2]) − (3.26 * Hypertension) − (0.61 * HbA1c [%]).

Follow-up and study endpoint

Follow-up duration was 48 months post-discharge or until patient death. Major adverse cardio-cerebral events (MACCEs), comprising all-cause death, non-fatal myocardial infarction (MI), non-fatal ischemic stroke and ischemia-induced revascularization, were defined as the primary endpoint. MI was reflected by cardiac enzyme levels above respective upper limits of their normal ranges, accompanied by ischemic symptoms or electrocardiogram changes suggestive of ischemia. Stroke was any ischemic cerebral infarction requiring hospitalization accompanied by overt neurological dysfunction, with lesions demonstrated on computed tomography (CT) or magnetic resonance (MR) images of the brain. Ischemia-induced revascularization referred to the revascularization of target and/or non-target vessels resulting from repeated or chronic ischemia.

Statistical analysis

All 2308 patients were divided into 4 groups ($eGDR_{WC}$: low eGDR [eGDR ≤ 7.05], high eGDR [eGDR > 7.05]; $eGDR_{BMI}$: low eGDR [eGDR ≤ 6.90] and high eGDR [eGDR > 6.90]) according to the medians of $eGDR_{WC}$ and $eGDR_{BMI}$, respectively.

Normally distributed continuous variates are mean ± standard deviation, and were assessed by independent samples t test. Continuous variates showing non-normal distribution were presented as median with 25th and 75th percentiles, and the Mann-Whitney U test was utilized for comparison between the two groups. Categorical variates were presented as

number and percentage, and the Chi-square, continuity-adjusted chi-square and Fisher's exact tests were performed for comparisons.

Kaplan-Meier curve analysis was carried out for describing the cumulative rates of MACCEs (primary study endpoint) at different levels of eGDR, with the log-rank test used for comparisons. Univariate Cox regression analysis was utilized for initially identifying potential risk factors for MACCEs. Variates determined as potential risk factors for the primary study endpoint in univariable analysis ($P < 0.05$) and potentially meaningful according to clinical practice were further examined in five multivariable models, and those with possible collinearity were excluded. eGDR was assessed with nominal and continuous variates, respectively. Hazard ratios (HRs) and 95% confidence intervals (CIs) were determined. In multivariate Cox proportional hazards analysis, five models were built for assessing eGDR's predictive value in the primary endpoint with the following adjustments: Model 1, age and sex; Model 2, Model 1 variates in addition to diabetes, hyperlipidemia, and previous MI, PCI and stroke; Model 3, Model 2 parameters in addition to triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), eGFR, fasting blood glucose (FBG), and left ventricular ejection fraction (LVEF); Model 4, Model 3 parameters and angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), oral hypoglycemic agent (OHA) and insulin uses at discharge; Model 5, Model 4 parameters in addition to left main artery (LM) lesion, multivessel lesion, in-stent restenosis, chronic total occlusion (CTO) lesion, SYNTAX score, LM lesion treatment, left circumflex artery (LCX) treatment, right coronary artery (RCA) treatment, complete revascularization and amount of used drug-eluting stent (DES).

On the basis of Model 5, the dose-response association of eGDR with the primary endpoint was represented by a restrictive cubic spline curve. Likelihood ratio tests were used to examine the nonlinearity hypothesis. Subsequent stratification was performed based on sex, age, smoking history, hyperlipidemia, diabetes, OHA at admission and insulin at admission to determine the consistency of eGDR in predicting MACCEs; the stratified analysis was adjusted for Model 5 variates.

The incremental effect of eGDR on the predictive power of currently recognized CVD risk factors in the primary endpoint were illustrated by Harrell's C-index, net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

Data analysis was carried out with SPSS v26.0 and R3.6.3. Two-tailed $P < 0.05$ was considered statistically significant.

Results

Baseline patient features

Totally 2308 cases were enrolled, averaging 60.09 ± 8.96 years old with a male ratio of 71.8% (n = 1658). According to median eGDR, individuals were separated into the low eGDR and high eGDR groups. Demographic, clinical and laboratory data, and details of drug and interventional therapies in the two groups of $eGDR_{WC}$ and $eGDR_{BMI}$ are presented in Table 1 and Table 2.

Table 1
Baseline characteristics of the study population in two groups of $eGDR_{WC}$

	Total population (n = 2308)	Lower eGDR (≤ 7.05; n = 1156)	Higher eGDR (> 7.05; n = 1152)	*P* value
Age, years	60.09 ± 8.96	60.21 ± 8.80	59.97 ± 9.12	0.525
Sex, male, n (%)	1658 (71.8)	852 (73.7)	806 (70.0)	0.046
BMI, kg/m^2	26.09 ± 3.20	27.53 ± 2.89	24.64 ± 2.81	< 0.001
WC, cm	91.42 ± 12.38	97.44 ± 10.62	85.37 ± 10.99	< 0.001
Heart rate, bpm	69.67 ± 10.13	70.47 ± 10.44	68.87 ± 9.76	< 0.001
SBP, mmHg	130.27 ± 16.45	133.00 ± 16.93	127.53 ± 15.48	< 0.001
DBP, mmHg	76.99 ± 9.77	78.35 ± 10.24	75.61 ± 9.06	< 0.001
Smoking history, n (%)	1309 (56.7)	674 (58.3)	635 (55.1)	0.123
Drinking history, n (%)	536 (23.2)	280 (24.2)	256 (22.2)	0.255
Family history of CAD, n (%)	236 (10.2)	118 (10.2)	118 (10.2)	0.978
Medical history, n (%)				
Diabetes	798 (34.6)	560 (48.4)	238 (20.7)	< 0.001
Hypertension	1436 (62.2)	1120 (96.9)	316 (27.4)	< 0.001
Hyperlipidemia	1986 (86.0)	1026 (88.8)	960 (83.3)	< 0.001
Previous MI	484 (21.0)	245 (21.2)	239 (20.7)	0.792
Previous PCI	382 (16.6)	199 (17.2)	183 (15.9)	0.390
Previous stroke	264 (11.4)	172 (14.9)	92 (8.0)	< 0.001
Previous PAD	79 (3.4)	40 (3.5)	39 (3.4)	0.921
Clinical diagnosis, n (%)				0.072
UA	1921 (83.2)	946 (81.8)	975 (84.6)	
NSTEMI	387 (16.8)	210 (18.2)	177 (15.4)	
Laboratory examinations				
TG, mmol/L	1.48 (1.05, 2.10)	1.61 (1.14, 2.27)	1.37 (0.98, 1.93)	< 0.001
TC, mmol/L	4.03 (3.40, 4.72)	4.01 (3.35, 4.73)	4.05 (3.44, 4.72)	0.268

$eGDR_{WC}$ estimated glucose disposal rate calculated by waist circumference, *BMI* body mass index, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CAD* coronary artery disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PAD* peripheral artery disease, *UA* unstable angina, *NSTEMI* non-ST-segment elevation myocardial infarction, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *eGFR* estimated glomerular filtration rate, *FBG* fasting blood glucose, *HbA1c* glycosylated hemoglobin A1c, *LVEF* left ventricular ejection fraction, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *DAPT* dual antiplatelet therapy, *OHA* oral hypoglycemic agents, *LM* left main artery, *SYNTAX* synergy between PCI with taxus and cardiac surgery, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *DES* drug-eluting stent

	Total population (n = 2308)	Lower eGDR (≤ 7.05; n = 1156)	Higher eGDR (> 7.05; n = 1152)	*P* value
LDL-C, mmol/L	2.39 (1.89, 2.98)	2.38 (1.88, 2.98)	2.41 (1.89, 2.99)	0.501
HDL-C, mmol/L	0.99 ± 0.23	0.95 ± 0.22	1.02 ± 0.24	< 0.001
hs-CRP, mg/L	1.27 (0.58, 3.30)	1.56 (0.71, 3.74)	1.04 (0.46, 2.74)	< 0.001
Creatinine, μmol/L	75.83 ± 16.52	77.43 ± 17.46	74.23 ± 15.37	< 0.001
eGFR, mL/(min × 1.73m^2)	93.57 ± 19.97	92.19 ± 20.43	94.96 ± 19.40	0.001
Uric acid, μmol/L	344.67 ± 80.75	352.94 ± 81.92	336.37 ± 78.73	< 0.001
FBG, mmol/L	6.13 ± 1.91	6.56 ± 2.22	5.69 ± 1.41	< 0.001
HbA1c, %	6.27 ± 1.19	6.61 ± 1.32	5.92 ± 0.93	< 0.001
LVEF, %	64.01 ± 6.72	63.90 ± 6.61	64.12 ± 6.82	0.424
Medication at admission, n (%)				
ACEI/ARB	511 (22.1)	385 (33.3)	126 (10.9)	< 0.001
DAPT	693 (30.0)	347 (30.0)	346 (30.0)	0.003
Aspirin	1220 (52.9)	611 (52.9)	609 (52.9)	0.996
P2Y12 inhibitors	738 (32.0)	364 (31.5)	374 (32.5)	0.615
β-Blocker	505 (21.9)	279 (24.1)	226 (19.6)	0.009
Statins	707 (30.6)	330 (28.5)	377 (32.7)	0.029
OHA	413 (17.9)	303 (26.2)	110 (9.5)	< 0.001
Insulin	225 (9.7)	159 (13.8)	66 (5.7)	< 0.001
Medication at discharge, n (%)				
ACEI/ARB	1602 (69.4)	1109 (95.9)	493 (42.8)	< 0.001
DAPT	2306 (99.9)	1155 (99.9)	1151 (99.9)	0.998
Aspirin	2307 (100.0)	1155 (99.9)	1152 (100.0)	0.318
P2Y12 inhibitors	2308 (100.0)	1156 (100.0)	1152 (100.0)	
β-Blocker	2095 (90.8)	1067 (92.3)	1028 (90.8)	0.011
Statins	2256 (97.7)	1129 (97.7)	1127 (97.8)	0.789

eGDR$_{WC}$ estimated glucose disposal rate calculated by waist circumference, *BMI* body mass index, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CAD* coronary artery disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PAD* peripheral artery disease, *UA* unstable angina, *NSTEMI* non-ST-segment elevation myocardial infarction, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *eGFR* estimated glomerular filtration rate, *FBG* fasting blood glucose, *HbA1c* glycosylated hemoglobin A1c, *LVEF* left ventricular ejection fraction, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *DAPT* dual antiplatelet therapy, *OHA* oral hypoglycemic agents, *LM* left main artery, *SYNTAX* synergy between PCI with taxus and cardiac surgery, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *DES* drug-eluting stent

	Total population (n = 2308)	Lower eGDR (≤ 7.05; n = 1156)	Higher eGDR (> 7.05; n = 1152)	*P* value
OHA	409 (17.7)	299 (25.9)	110 (9.5)	< 0.001
Insulin	217 (9.4)	151 (13.1)	66 (5.7)	< 0.001
Angiographic data, n (%)				
LM lesion	103 (4.5)	56 (4.8)	47 (4.1)	0.374
Multi-vessel lesion	1536 (66.6)	853 (73.8)	683 (59.3)	< 0.001
In-stent restenosis	125 (5.4)	64 (5.5)	61 (5.3)	0.798
Chronic total occlusion lesion	299 (13.0)	164 (14.2)	135 (11.7)	0.077
SYNTAX score	10.61 ± 5.45	11.29 ± 5.58	9.93 ± 5.24	< 0.001
Procedural information				
Target vessel territory, n (%)				
LM	60 (2.6)	30 (2.6)	30 (2.6)	0.989
LAD	1506 (65.3)	731 (63.2)	775 (67.3)	0.042
LCX	804 (34.8)	437 (37.8)	367 (31.9)	0.003
RCA	978 (42.2)	539 (46.6)	439 (38.1)	< 0.001
Complete revascularization, n (%)	1363 (59.1)	628 (54.3)	735 (63.8)	< 0.001
Number of DES	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	2.00 (1.00, 2.00)	0.003

eGDR$_{WC}$ estimated glucose disposal rate calculated by waist circumference, *BMI* body mass index, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CAD* coronary artery disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PAD* peripheral artery disease, *UA* unstable angina, *NSTEMI* non-ST-segment elevation myocardial infarction, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *eGFR* estimated glomerular filtration rate, *FBG* fasting blood glucose, *HbA1c* glycosylated hemoglobin A1c, *LVEF* left ventricular ejection fraction, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *DAPT* dual antiplatelet therapy, *OHA* oral hypoglycemic agents, *LM* left main artery, *SYNTAX* synergy between PCI with taxus and cardiac surgery, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *DES* drug-eluting stent

Table 2
Baseline characteristics of the study population in two groups of $eGDR_{BMI}$

	Total population (n = 2308)	Lower eGDR (≤ 6.90; n = 1152)	Higher eGDR (> 6.90; n = 1156)	*P* value
Age, years	60.09 ± 8.96	60.24 ± 8.74	59.94 ± 9.17	0.424
Sex, male, n (%)	1658 (71.8)	782 (67.9)	876 (75.8)	< 0.001
BMI, kg/m^2	26.09 ± 3.20	27.48 ± 2.82	24.70 ± 2.94	< 0.001
WC, cm	91.42 ± 12.38	96.44 ± 11.18	86.41 ± 11.45	< 0.001
Heart rate, bpm	69.67 ± 10.13	70.49 ± 10.30	68.87 ± 9.91	< 0.001
SBP, mmHg	130.27 ± 16.45	133.26 ± 17.15	127.29 ± 15.14	< 0.001
DBP, mmHg	76.99 ± 9.77	78.21 ± 10.28	75.77 ± 9.07	< 0.001
Smoking history, n (%)	1309 (56.7)	634 (55.0)	675 (58.4)	0.104
Drinking history, n (%)	536 (23.2)	254 (22.0)	282 (24.4)	0.182
Family history of CAD, n (%)	236 (10.2)	121 (10.5)	115 (9.9)	0.660
Medical history, n (%)				
Diabetes	798 (34.6)	563 (48.9)	235 (20.3)	< 0.001
Hypertension	1436 (62.2)	1133 (98.4)	303 (26.2)	< 0.001
Hyperlipidemia	1986 (86.0)	1025 (89.0)	961 (83.1)	< 0.001
Previous MI	484 (21.0)	232 (20.1)	252 (21.8)	0.327
Previous PCI	382 (16.6)	199 (17.3)	183 (15.8)	0.351
Previous stroke	264 (11.4)	168 (14.6)	96 (8.3)	< 0.001
Previous PAD	79 (3.4)	39 (3.4)	40 (3.5)	0.921
Clinical diagnosis, n (%)				0.227
UA	1921 (83.2)	948 (82.3)	973 (84.2)	
NSTEMI	387 (16.8)	204 (17.7)	183 (15.8)	
Laboratory examinations				
TG, mmol/L	1.48 (1.05, 2.10)	1.62 (1.17, 2.24)	1.36 (0.96, 1.93)	< 0.001
TC, mmol/L	4.03 (3.40, 4.72)	4.03 (3.39, 4.74)	4.02 (3.42, 4.70)	0.923

$eGDR_{BMI}$ estimated glucose disposal rate calculated body mass index, *BMI* body mass index, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CAD* coronary artery disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PAD* peripheral artery disease, *UA* unstable angina, *NSTEMI* non-ST-segment elevation myocardial infarction, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *eGFR* estimated glomerular filtration rate, *FBG* fasting blood glucose, *HbA1c* glycosylated hemoglobin A1c, *LVEF* left ventricular ejection fraction, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *DAPT* dual antiplatelet therapy, *OHA* oral hypoglycemic agents, *LM* left main artery, *SYNTAX* synergy between PCI with taxus and cardiac surgery, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *DES* drug-eluting stent

	Total population (n = 2308)	Lower eGDR (≤ 6.90; n = 1152)	Higher eGDR (> 6.90; n = 1156)	*P* value
LDL-C, mmol/L	2.39 (1.89, 2.98)	2.40 (1.89, 2.99)	2.38 (1.88, 2.97)	0.663
HDL-C, mmol/L	0.99 ± 0.23	0.95 ± 0.22	1.02 ± 0.24	< 0.001
hs-CRP, mg/L	1.27 (0.58, 3.30)	1.54 (0.71, 3.74)	1.05 (0.46, 2.76)	< 0.001
Creatinine, μmol/L	75.83 ± 16.52	76.26 ± 17.23	75.41 ± 15.79	0.219
eGFR, mL/(min × 1.73m^2)	93.57 ± 19.97	92.17 ± 20.33	94.98 ± 19.50	0.001
Uric acid, μmol/L	344.67 ± 80.75	349.44 ± 82.16	339.91 ± 79.07	0.005
FBG, mmol/L	6.13 ± 1.91	6.54 ± 2.18	5.72 ± 1.49	< 0.001
HbA1c, %	6.27 ± 1.19	6.62 ± 1.31	5.92 ± 0.94	< 0.001
LVEF, %	64.01 ± 6.72	64.07 ± 6.56	63.95 ± 6.87	0.660
Medication at admission, n (%)				
ACEI/ARB	511 (22.1)	390 (33.9)	121 (10.5)	< 0.001
DAPT	693 (30.0)	343 (29.8)	350 (30.3)	0.792
Aspirin	1220 (52.9)	597 (51.8)	623 (53.9)	0.319
P2Y12 inhibitors	738 (32.0)	360 (31.3)	378 (32.7)	0.455
β-Blocker	505 (21.9)	283 (24.6)	222 (19.2)	0.002
Statins	707 (30.6)	330 (28.6)	377 (32.6)	0.039
OHA	413 (17.9)	302 (26.2)	111 (9.6)	< 0.001
Insulin	225 (9.7)	161 (14.0)	64 (5.5)	< 0.001
Medication at discharge, n (%)				
ACEI/ARB	1602 (69.4)	1115 (96.8)	487 (42.1)	< 0.001
DAPT	2306 (99.9)	1151 (99.9)	1155 (99.9)	0.998
Aspirin	2307 (100.0)	1151 (99.9)	1156 (100.0)	0.316
P2Y12 inhibitors	2308 (100.0)	1152 (100.0)	1156 (100.0)	
β-Blocker	2095 (90.8)	1068 (92.7)	1027 (88.8)	0.001
Statins	2256 (97.7)	1127 (97.8)	1129 (97.7)	0.789

$eGDR_{BMI}$ estimated glucose disposal rate calculated body mass index, *BMI* body mass index, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CAD* coronary artery disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PAD* peripheral artery disease, *UA* unstable angina, *NSTEMI* non-ST-segment elevation myocardial infarction, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *eGFR* estimated glomerular filtration rate, *FBG* fasting blood glucose, *HbA1c* glycosylated hemoglobin A1c, *LVEF* left ventricular ejection fraction, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *DAPT* dual antiplatelet therapy, *OHA* oral hypoglycemic agents, *LM* left main artery, *SYNTAX* synergy between PCI with taxus and cardiac surgery, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *DES* drug-eluting stent

	Total population (n = 2308)	Lower eGDR (≤ 6.90; n = 1152)	Higher eGDR (> 6.90; n = 1156)	*P* value
OHA	409 (17.7)	298 (25.9)	111 (9.6)	< 0.001
Insulin	217 (9.4)	153 (13.3)	64 (5.5)	< 0.001
Angiographic data, n (%)				
LM lesion	103 (4.5)	52 (4.5)	51 (4.4)	0.905
Multi-vessel lesion	1536 (66.6)	852 (74.0)	684 (59.2)	< 0.001
In-stent restenosis	125 (5.4)	67 (5.8)	58 (5.0)	0.397
Chronic total occlusion lesion	299 (13.0)	152 (13.2)	147 (12.7)	0.732
SYNTAX score	10.61 ± 5.45	11.26 ± 5.48	9.97 ± 5.36	< 0.001
Procedural information				
Target vessel territory, n (%)				
LM	60 (2.6)	28 (2.4)	32 (2.8)	0.610
LAD	1506 (65.3)	733 (63.6)	773 (66.9)	0.102
LCX	804 (34.8)	434 (37.7)	370 (32.0)	0.004
RCA	978 (42.2)	536 (46.5)	442 (38.2)	< 0.001
Complete revascularization, n (%)	1363 (59.1)	624 (54.2)	739 (63.9)	< 0.001
Number of DES	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	2.00 (1.00, 2.00)	0.001

eGDR$_{BMI}$ estimated glucose disposal rate calculated body mass index, *BMI* body mass index, *WC* waist circumference, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *CAD* coronary artery disease, *MI* myocardial infarction, *PCI* percutaneous coronary intervention, *PAD* peripheral artery disease, *UA* unstable angina, *NSTEMI* non-ST-segment elevation myocardial infarction, *TG* triglyceride, *TC* total cholesterol, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *eGFR* estimated glomerular filtration rate, *FBG* fasting blood glucose, *HbA1c* glycosylated hemoglobin A1c, *LVEF* left ventricular ejection fraction, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *DAPT* dual antiplatelet therapy, *OHA* oral hypoglycemic agents, *LM* left main artery, *SYNTAX* synergy between PCI with taxus and cardiac surgery, *LAD* left anterior descending artery, *LCX* left circumflex artery, *RCA* right coronary artery, *DES* drug-eluting stent

For eGDR$_{WC}$, an elevated rate of male participants was found in cases with low eGDR in comparison with those with high eGDR. The low eGDR group showed elevated BMI, WC, heart rate, systolic blood pressure, diastolic blood pressure and incidences of T2DM, hypertension, hyperlipidemia and previous stroke. Patients with low eGDR had higher levels of TG, creatinine, high-sensitivity C-reactive protein, uric acid, FBG and HbA1c, and reduced HDL-C and eGFR amounts. Concerning drugs administered at admission, the low eGDR group had elevated proportions of ACEI/ARB, dual antiplatelet therapy (DAPT), β-Blocker, OHA and insulin therapies, and reduced statin rate; meanwhile, patients in the low eGDR group had higher odds of being prescribed ACEI/ARB, β-blockers, OHA and insulin. Based on coronary angiography and PCI, the proportion of multivessel disease and the SYNTAX score were elevated in the low eGDR group. The low eGDR group was more likely to show LCX and RCA target vessels with treatment and DES implantation, and lower proportions of left anterior descending artery (LAD) treatment and complete revascularization.

For $eGDR_{BMI}$, the baseline patient features were consistent with $eGDR_{WC}$, except that the low eGDR group had a lower proportion of males, with no statistically significant differences in creatinine, DAPT at admission and LAD treatment.

Incidence of the primary endpoint

During the follow-up, 547 patients (23.7%) had MACCEs, comprising 36 (1.6%) all-cause deaths, 112 (4.9%) non-fatal MI cases, 45 (1.9%) non-fatal ischemic strokes and 354 (15.3%) ischemia-induced revascularization cases.

For $eGDR_{WC}$, MACCE ($P < 0.001$), non-fatal MI ($P = 0.007$), non-fatal ischemic stroke ($P = 0.001$) and ischemia-induced revascularization ($P < 0.001$) rates were markedly elevated in cases with low eGDR in comparison with those with high eGDR. However, all-cause mortality rates were comparable in both groups (Table 3).

Table 3
Incidence of primary endpoint and each component according to the median of $eGDR_{WC}$

	Total population (n = 2308)	Lower eGDR (≤ 7.05; n = 1156)	Higher eGDR (> 7.05; n = 1152)	*P* value
MACCE, n (%)	547 (23.7)	345 (29.8)	202 (17.5)	< 0.001
All-cause death, n (%)	36 (1.6)	20 (1.7)	16 (1.4)	0.508
Non-fatal MI, n (%)	112 (4.9)	70 (6.1)	42 (3.6)	0.007
Non-fatal ischemic stroke, n (%)	45 (1.9)	34 (2.9)	11 (1.0)	0.001
Ischemia-driven revascularization, n (%)	354 (15.3)	221 (19.1)	133 (11.5)	< 0.001

$eGDR_{WC}$ estimated glucose disposal rate calculated by waist circumference, *eGDR* estimated glucose disposal rate, *MACCE* major adverse cardio-cerebral events, *MI* myocardial infarction

For $eGDR_{BMI}$, cases with low eGDR showed higher rates of MACCEs ($P < 0.001$), non-fatal ischemic stroke ($P = 0.010$) and ischemia-induced revascularization ($P < 0.001$). Both groups were comparable in all-cause death and non-fatal MI rates (Table 4).

Table 4
Incidence of primary endpoint and each component according to the median of $eGDR_{BMI}$

	Total population (n = 2308)	Lower eGDR (≤ 6.90; n = 1152)	Higher eGDR (> 6.90; n = 1156)	*P* value
MACCE, n (%)	547 (23.7)	320 (27.8)	227 (19.6)	< 0.001
All-cause death, n (%)	36 (1.6)	17 (1.5)	19 (1.6)	0.745
Non-fatal MI, n (%)	112 (4.9)	64 (5.6)	48 (4.2)	0.117
Non-fatal ischemic stroke, n (%)	45 (1.9)	31 (2.7)	14 (1.2)	0.010
Ischemia-driven revascularization, n (%)	354 (15.3)	208 (18.1)	146 (12.6)	< 0.001

$eGDR_{BMI}$ estimated glucose disposal rate calculated by body mass index, *eGDR* estimated glucose disposal rate, *MACCE* major adverse cardio-cerebral events, *MI* myocardial infarction

Cumulative risk of primary endpoint at follow-up

Kaplan-Meier curve analysis was utilized for assessing the cumulative incidence of MACCEs in the overall, diabetic and non-diabetic cohorts.

For $eGDR_{WC}$, the cumulative incidence of the primary endpoint was markedly elevated in cases with low eGDR in comparison with those with high eGDR in the general (Fig. 2A, log-rank $P < 0.001$), diabetic (Fig. 2B, log-rank $P = 0.004$) and non-diabetic (Fig. 2C, log-rank $P < 0.001$) cohorts. For $eGDR_{BMI}$, the incidence of the primary endpoint was elevated in cases with low eGDR in the general (Fig. 2D, log-rank $P < 0.001$) and non-diabetic (Fig. 2F, log-rank $P = 0.001$) cohorts, while in the diabetic population (Fig. 2E, log-rank $P = 0.154$), comparable rates were found in both groups.

Predictive value of eGDR for MACCEs

We included variates and built five multivariate models for assessing the predictive potential of eGDR for the primary endpoint (shown in Methods). Univariable Cox proportional hazards analyses to initially determine predictive factors of MACCEs are summarized in Supplementary Table 1. For $eGDR_{WC}$, eGDR had an independent prognostic value with significance in five models, both nominal and continuous. However, for $eGDR_{BMI}$, eGDR showed an independent predictive potential only in Models 1 and 2, and not in Models 3–5 (Table 5).

Table 5
Predictive value of eGDR for the risk of primary endpoint

	$eGDR_{WC}$				$eGDR_{BMI}$			
	As nominal variate[a]		As continuous variate[b]		As nominal variate[a]		As continuous variate[b]	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Unadjusted	1.814 (1.525–2.158)	< 0.001	1.195 (1.149–1.242)	< 0.001	1.478 (1.247–1.752)	< 0.001	1.131 (1.083–1.180)	< 0.001
Model 1	1.820 (1.529–2.165)	< 0.001	1.204 (1.157–1.253)	< 0.001	1.468 (1.237–1.741)	< 0.001	1.128 (1.079–1.178)	0.001
Model 2	1.630 (1.357–1.958)	< 0.001	1.181 (1.131–1.234)	< 0.001	1.272 (1.061–1.524)	0.009	1.085 (1.034–1.138)	0.001
Model 3	1.448 (1.202–1.744)	< 0.001	1.140 (1.090–1.191)	< 0.001	1.153 (0.960–1.385)	0.128	1.044 (0.994–1.096)	0.084
Model 4	1.459 (1.168–1.821)	0.001	1.179 (1.115–1.246)	< 0.001	1.053 (0.848–1.309)	0.640	1.015 (0.952–1.083)	0.639
Model 5	1.351 (1.086–1.681)	0.007	1.152 (1.088–1.219)	< 0.001	1.040 (0.837–1.293)	0.722	0.998 (0.936–1.064)	0.957
Model 1: adjusted for age, sex								
Model 2: adjusted for variates in Model 1 and diabetes, hyperlipidemia, previous MI, previous PCI, previous stroke								
Model 3: adjusted for variates in Model 2 and TG, TC, HDL-C, eGFR, FBG, LVEF								
Model 4: adjusted for variates in Model 3 and ACEI/ARB at discharge, OHA at discharge, insulin at discharge								
Model 5: adjusted for variates in Model 4 and LM lesion, multi-vessel lesion, in-stent restenosis, chronic total occlusion lesion, SYNTAX score, LM treatment, LCX treatment, RCA treatment, complete revascularization, number of DES								
[a]The HR was evaluated regarding the higher median of eGDR as reference								
[b]The HR was evaluated by per 1-unit decrease of eGDR								
$eGDR_{WC}$ estimated glucose disposal rate calculated by waist circumference, *$eGDR_{BMI}$* estimated glucose disposal rate calculated by body mass index, *HR* hazard ratio, *CI* confidence interval								

Dose-response association of $eGDR_{WC}$ with MACCEs

The dose-response association of $eGDR_{WC}$ with the primary endpoint was illustrated by generating a restricted cubic spline curve (Fig. 3). The risk of MACCEs was found to increase with $eGDR_{WC}$ ($P < 0.001$ for the overall association), suggesting a linear association of $eGDR_{WC}$ with the risk of MACCEs. The above finding was verified by the nonlinear correlation test ($P < 0.001$ for nonlinear correlation).

Stratified analysis of $eGDR_{WC}$

$eGDR_{WC}$'s predictive power for the risk of MACCEs did not differ across subgroups based on sex (male or female), age (< 65 or ≥ 65 years), smoking history (no or yes), hyperlipidemia (no or yes), diabetes (no or yes), OHA at admission (no or yes) and insulin at admission (no or yes) (all *P* for interaction > 0.05), further confirming the potential of $eGDR_{WC}$ to predict MACCEs (Fig. 4).

eGDR enhances the predictive abilities of other parameters for MACCEs

In the baseline model encompassing cardiovascular risk factors (sex, age, smoking history, hyperlipidemia, diabetes, MI history, stroke history, eGFR, NSTEMI, LVEF, SYNTAX score, complete revascularization and amount of DES), addition of eGDRwc significantly improved the model's value in predicting risk (Harrell's C-index: eGDRwc, 0.778 versus Baseline model, 0.768, *P* = 0.003), as well as its reclassification and discrimination abilities (Continuous-NRI = 0.125, *P* < 0.001; IDI = 0.016, *P* < 0.001). However, adding $eGDR_{BMI}$ did not starkly increase the baseline model's predictive power (Harrell's C-index: $eGDR_{BMI}$, 0.769 versus Baseline model, 0.768, *P* = 0.198; Continuous NRI: 0.061, P = 0.066; IDI: 0.002, P = 0.126) (Table 6).

Table 6
Incremental effects of $eGDR_{WC}$ and $eGDR_{BMI}$ on risk stratification for the primary endpoint beyond existing risk factors

	Harrell's C-index			**Continuous-NRI**			**IDI**		
	Estimation	95% CI	*P* for comparison	Estimation	95% CI	*P* value	Estimation	95% CI	*P* value
Baseline model	0.768	0.750–0.786	-	-	-	-	-	-	-
$eGDR_{WC}$	0.778	0.760–0.796	0.003	0.125	0.067–0.176	< 0.001	0.016	0.008–0.027	< 0.001
$eGDR_{BMI}$	0.769	0.751–0.788	0.198	0.061	-0.009-0.109	0.066	0.002	0.000-0.006	0.126

NRI net reclassification improvement, *IDI* integrated discrimination improvement, *CI* confidence interval

$eGDR_{WC}$ estimated glucose disposal rate calculated by waist circumference, *$eGDR_{BMI}$* estimated glucose disposal rate calculated by body mass index,

Discussion

The current work mainly assessed eGDR's predictive value for negative outcome after PCI in NSTE-ACS patients. It demonstrated that low eGDR was highly associated with elevated incidence of the primary endpoint. Reduction in eGDR levels represented a significant and independent predictive factor of adverse outcome in the examined study population. Moreover, compared with eGDR calculated by BMI, eGDR calculated by WC was more potent in predicting poor prognosis after PCI in NSTE-ACS individuals. Furthermore, addition of eGDR improved the ability of a model incorporating currently recognized cardiovascular risk factors for predicting a negative prognosis.

IR is the most critical mechanism of T2DM progression. IR is tightly correlated with the onset, progression and long-term prognosis of CVD as demonstrated recently. Data have confirmed that IR is significantly correlated with the formation of atherosclerotic plaques and cardiac dysfunction [33], in agreement with previous studies revealing that IR has profound

effects in the whole process of CVD [34, 35]. Additionally, IR is significantly linked to adverse patient outcome in individuals with pre-existing CVD [36, 37]. Therefore, accurate and efficient assessment of IR has important clinical value for predicting the progression and prognosis of CVD, especially coronary heart disease. Although direct assessment methods including hyperinsulinemic-euglycemic clamp, insulin suppression test and minimal model analysis of the insulin-modified frequently sampled intravenous glucose tolerance test can accurately assess IR, they have high operational complexity and invasive properties, precluding their wide application in clinical practice. Therefore, in recent years, clinicians have attempted to develop simple surrogate indicators of IR.

eGDR was developed and validated by the hyperinsulinemic-euglycemic clamp, which ensures its accuracy for the assessment of IR to a certain extent. IR assessed by eGDR is considered the only factor consistently associated with all chronic complications of T1DM [38]. A cross-sectional study of T1DM patients found that individuals showing low eGDR have remarkably enhanced risk of CVD [39]. In T1DM, eGDR was shown to be an effective predictor of survival with tight associations with all-cause mortality and cardiovascular mortality [40]. In T2DM cases, eGDR was found to independently predict all-cause mortality upon adjustment for confounders such as diabetic kidney disease [41]. Furthermore, eGDR is also considered a reliable, clinically applicable method for the assessment of double diabetes and could be used to monitor response to specific treatments, with an effect similar to that of HbA1c [11]. As stated in the introduction, in a nationwide observational study of 3256 individuals with T2DM who underwent CABG with a median follow-up of 3.1 years, low eGDR was strongly associated with enhanced risk of all-cause mortality, independently of other cardiac vascular and metabolic risk factors [21]. In addition, in another observational cohort trial of 104697 T2DM cases with a 5.6-year median follow-up, low eGDR was associated with escalated incidence rates of stroke and mortality, indicating eGDR might serve as a risk marker of stroke and death [42]. These findings suggest that eGDR has great potential for predicting the prognosis of patients with cardio-cerebral diseases. Based on the above studies, this work also obtained consistent findings, further clarifying the predictive potential of eGDR reduction for adverse consequence in NSTE-ACS individuals treated by PCI. Multivariate and subgroup analysis suggested that eGDR was a strong and stable predictor of adverse events. This study also found that $eGDR_{WC}$ was more robust than $eGDR_{BMI}$ in multivariate analysis. Moreover, the incremental effect of $eGDR_{WC}$ on the predictive ability of CVD predictors for the primary endpoint was stronger than that of $eGDR_{BMI}$. BMI is a currently recognized cardiovascular risk factor [43]. WC, which reflects visceral fat, is strongly associated with IR and ASCVD progression [44]. Whether the prognostic value of $eGDR_{WC}$ in NSTE-ACS cases undergoing PCI is higher than that of $eGDR_{BMI}$ needs to be determined in larger and better-designed studies.

The calculation formula of eGDR includes three factors: hypertension, HbA1c and WC. Hypertension is the most important component of the formula [9], with a well-known impact on ASCVD development and prognosis. HbA1c is a known predictor of CAD severity and early prognosis in stable angina pectoris [45]. In diabetics with successful DES implantation, HbA1c is highly correlated with enhanced risk of major adverse cardiovascular events [46]. In obesity, it is highly related not only to IR, but also to underlying diseases such as hypertension, dyslipidemia, CVD and stroke [44, 47]. WC is the preferred index recommended by the World Health Organization for the evaluation of central obesity, showing a strong association with visceral fat content measured by CT. WC shows associations with the incidence rates of cardiac death and non-fatal MI in cases administered PCI [48]. For eGDR, IR assessed by eGDR is independently correlated with carotid plaque burden in T1DM [49]. In addition, a study examining the correlations between eGDR and thrombotic biomarkers in T1DM patients showed that eGDR is a suitable indicator of prothrombotic status, with superiority to BMI and insulin requirements [50].

The limitations of the current study should be addressed. First, given its single-center, retrospective, observational features, larger prospective multicenter trials are warranted to validate the present findings and improve the power of this analysis. Secondly, UA patients accounted for the majority of all NSTE-ACS cases in this study, so these results may

not reflect the prognostic potential of eGDR in NSTEMI patients. Finally, only Chinese individuals were included, and the generalizability and stability of the findings need to be verified in other ethnic groups.

Conclusions

In NSTE-ACS individuals undergoing PCI, low eGDR is strongly linked to high MACCE incidence and constitutes an independent predictor of adverse prognosis. eGDR highly enhances the ability of the currently accepted risk model to predict adverse consequences. $eGDR_{WC}$ has better predictive power than $eGDR_{BMI}$ in NSTE-ACS individuals undergoing PCI.

Abbreviations

CVD: cardiovascular disease; CAD: coronary artery disease; T2DM: type 2 diabetes mellitus; IR: insulin resistance; ROS: reactive oxygen species; eGDR: estimated glucose disposal rate; T1DM: type 1 diabetes mellitus; WHR: waist-to-hip ratio; HbA1c: glycosylated hemoglobin; WC: waist circumference; BMI: body mass index; ASCVD: atherosclerotic cardiovascular disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; CAD: coronary artery disease; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; NSTEMI: non-ST-segment elevation myocardial infarction; UA: unstable angina; eGFR: estimated glomerular filtration rate; PAD: peripheral arterial disease; SYNTAX: the synergy between PCI with taxus and cardiac surgery; $eGDR_{WC}$: eGDR calculated by WC; $eGDR_{BMI}$: eGDR calculated by BMI; MACCE: major adverse cardio-cerebral event; MI: myocardial infarction; CT: computed tomography; HR: hazard ratio; CI: confidence interval; TG: triglyceride; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; FBG: fasting blood glucose; LVEF: left ventricular ejection fraction; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; OHA: oral hypoglycemic agents; LM: left main artery; CTO: chronic total occlusion; LCX: left circumflex artery; RCA: right coronary artery; DES: drug-eluting stent; NRI: net reclassification improvement; IDI: integrated discrimination improvement; DAPT: dual antiplatelet therapy; LAD: left anterior descending artery;

Declarations

Ethical Approval and Consent to participate

This research protocol was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital, Capital Medical University. Although the study design was retrospective, participants provided written or verbal informed consent.

Consent for publication

Not applicable.

Availability of supporting data

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

CL and QZ made substantial contributions to study design, data collection, data analysis and manuscript writing. YJZ and XLL made substantial contributions to study design and intellectual direction. XTM, YJC, YS, DZ made contributions to data collection and analysis. All authors read and approved the final manuscript.

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Figures

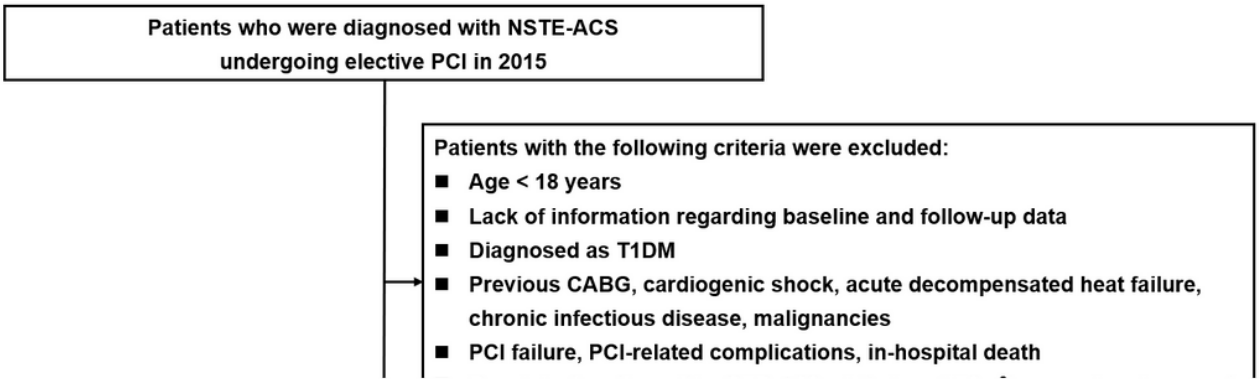

Figure 1

Flow diagram for the enrollment of study population.

NSTE-ACS non-ST-segment elevation acute coronary syndrome, *PCI* percutaneous coronary intervention, *T1DM* Type 1 Diabetes mellitus, *CABG* coronary artery bypass grafting, *eGFR* estimated glomerular filtration rate, *ALT* alanine transaminase, *AST* aspartate transaminase, *URL* upper reference limit, *eGDR* estimated glucose disposal rate, *WC* waist circumference, *BMI* body mass index

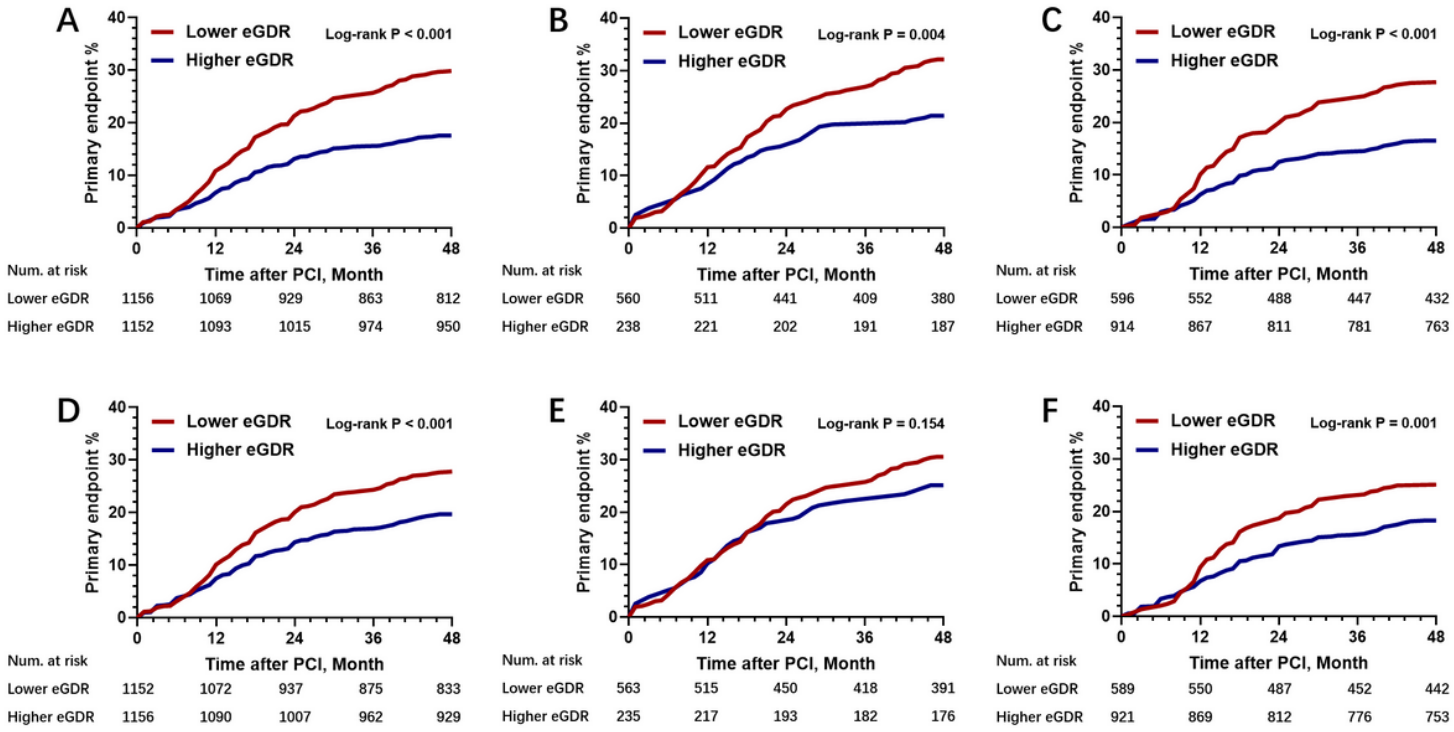

Figure 2

Kaplan-Meier survival curves according to the median of eGDR.

A Kaplan-Meier survival curve for the primary endpoint of the overall population in the two groups based on $eGDR_{WC}$; **B** Kaplan-Meier survival curve for the primary endpoint of the patients with diabetes in the two groups based on $eGDR_{WC}$; **C** Kaplan-Meier survival curve for the primary endpoint of the patients without diabetes in the two groups based on $eGDR_{WC}$; **D** Kaplan-Meier survival curve for the primary endpoint of the overall population in the two groups based on $eGDR_{BMI}$; **E** Kaplan-Meier survival curve for the primary endpoint of the patients with diabetes in the two groups based on $eGDR_{BMI}$; **F** Kaplan-Meier survival curve for the primary endpoint of the patients without diabetes in the two groups based on $eGDR_{BMI}$.

eGDR estimated glucose disposal rate

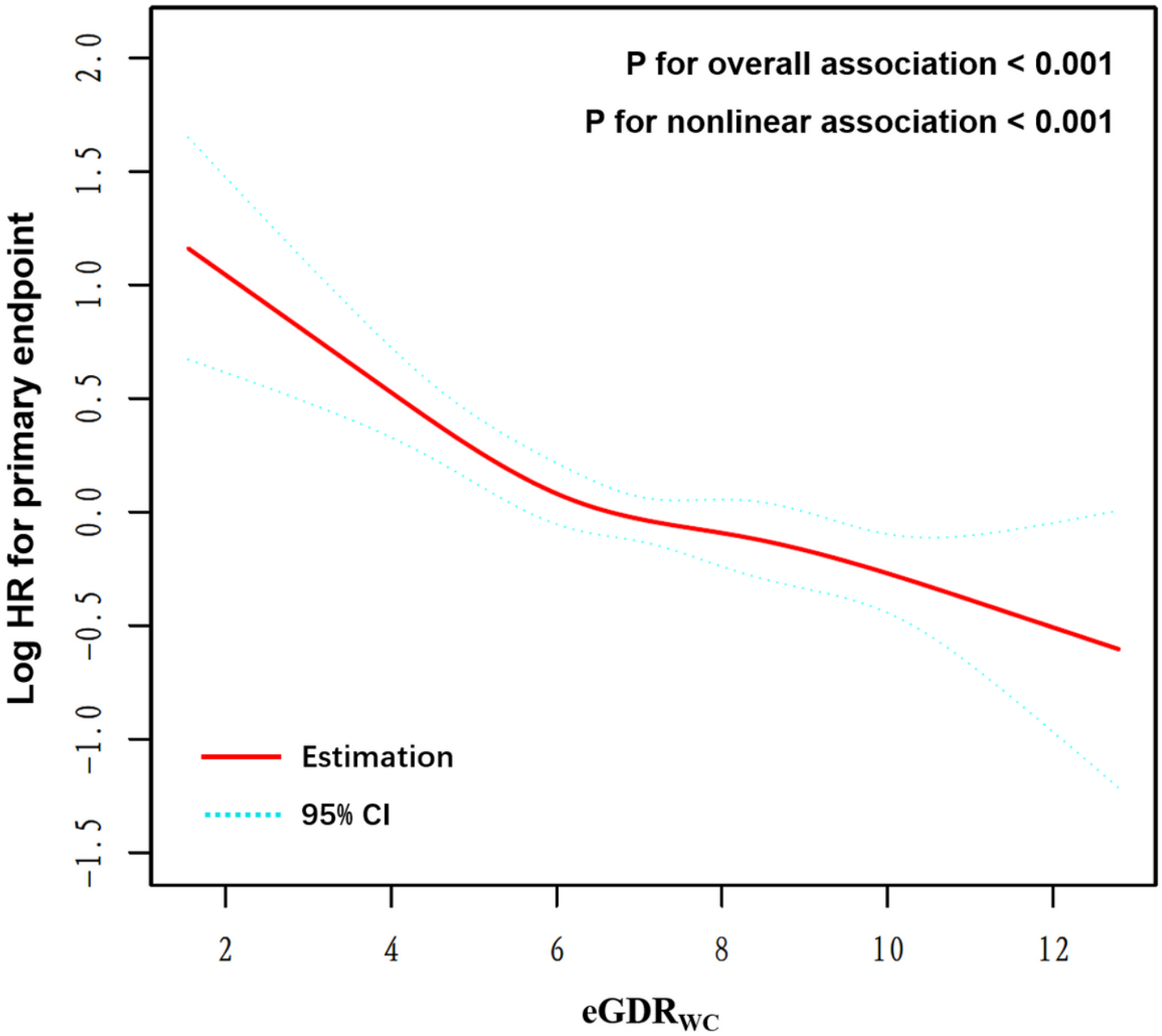

Figure 3

Restricted cubic smoothing for the risk of the primary endpoint according to the $eGDR_{WC}$.

The analysis was adjusted for Model 5.

HR was evaluated by per 1-unit increase of $eGDR_{WC}$.

$eGDR_{WC}$ estimated glucose disposal rate calculated by waist circumference

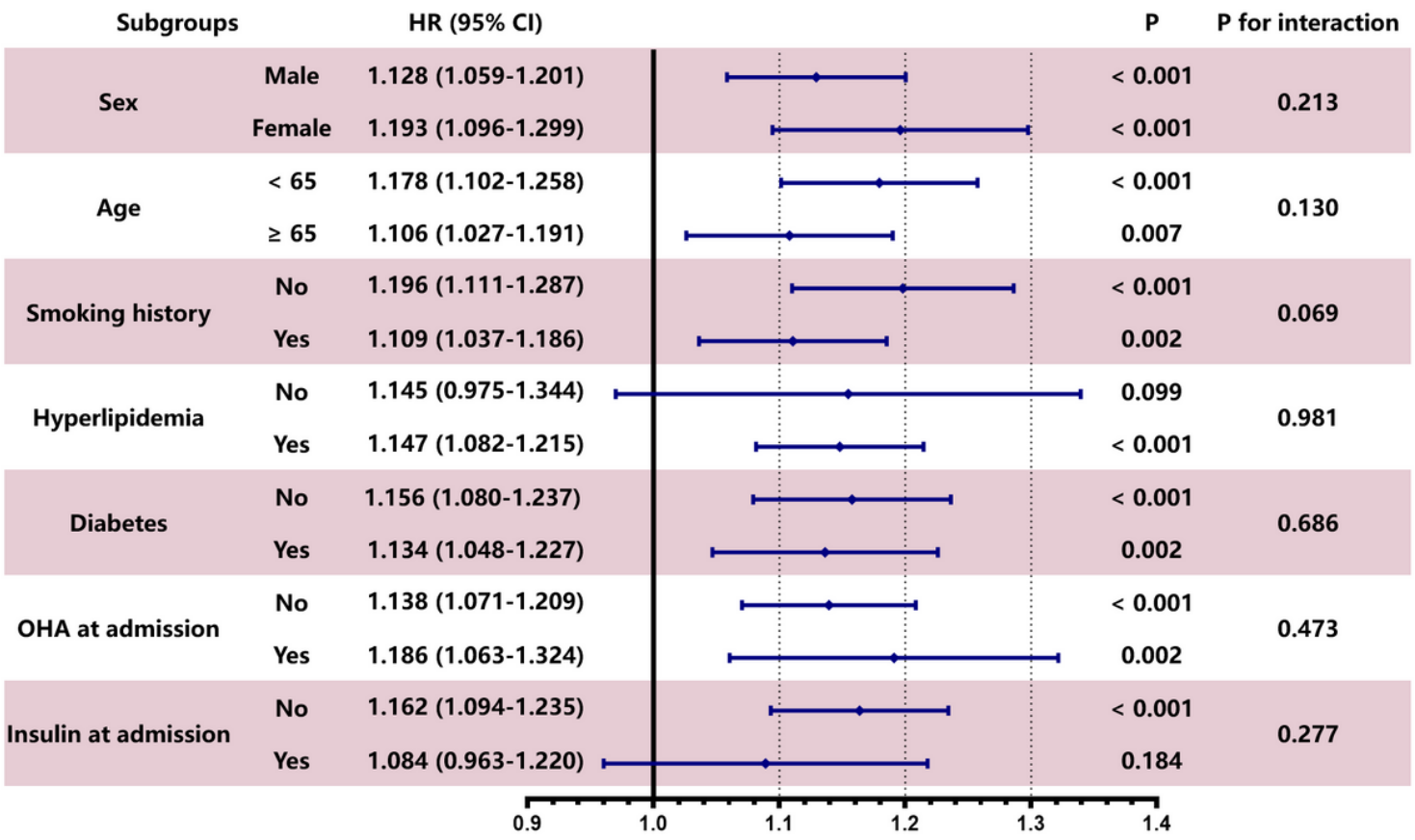

Figure 4

Subgroup analysis evaluating the robustness of $eGDR_{WC}$ in predicting the risk of the primary endpoint.

The analysis was adjusted for Model 5 except for variates applied for grouping.

HR was evaluated by per 1-unit decrease of $eGDR_{WC}$.

OHA oral hypoglycemic agents

Supplementary Files

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- additionalfile.docx