

# Fasting Blood Glucose to High-Density Lipoprotein Cholesterol Ratio in Relation to Short-Term Outcomes in Patients with Acute Coronary Syndrome

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## Research

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# Abstract

## Background

Biochemical markers are crucial for determining risk in patients with coronary artery disease (CAD); however, the association between the fasting blood glucose to high-density lipoprotein cholesterol (FG/HDL-C) ratio and short-term outcomes in patients with acute coronary syndrome (ACS) remains unknown. We investigated the association between the FG/HDL-C ratio and 30-day major adverse cardiovascular events (MACEs) and cardiovascular (CV) death in patients with ACS.

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## Methods

We performed a post-hoc analysis of data from the Acute Coronary Syndrome Quality Improvement in Kerala (ACS-QUIK) study. A total of 11,284 patients with ACS were subdivided into quartiles according to their FG/HDL-C ratios. We used a multivariate logistic regression model, generalized additive model (GAM), and two-piecewise linear regression model to determine the association of the FG/HDL-C ratio with MACEs (death, reinfarction, stroke, and major bleeding) and CV death.

## Results

The FG/HDL-C ratio was significantly associated with an increased risk of MACEs and CV death in patients with ACS in the highest quartile (MACEs, odds ratio [OR]: 1.49; 95% confidence interval [CI], [1.11, 1.99];  $P < 0.01$ ; CV death, OR: 1.69; 95% CI, [1.01, 1.41];  $P = 0.04$ ). The GAM and two-piecewise linear regression model demonstrated that the relationship between the FG/HDL-C ratio and MACEs and CV death was non-linear (non-linear  $P < 0.05$ ); the threshold values were 3.02 and 3.00 for MACEs and CV death, respectively.

## Conclusions

A higher FG/HDL-C ratio is associated with an increased risk of MACEs and CV death in patients with ACS.

## Background

Coronary artery disease (CAD) has complex pathophysiological features and is thought to be a multifactorial disease (1, 2). Globally, CAD contributes to one-third of deaths in people over the age of 35 years (3). In particular, among patients with CAD, acute coronary syndrome (ACS) is a serious concern because of adverse outcomes during the follow-up period, such as death, reinfarction, stroke, major bleeding, and cardiovascular (CV) death (4).

Metabolic syndrome (MetS) is known as the major etiological contributor to CAD (5), despite the existence of several different definitions of MetS; however, these differences are minor. MetS is characterized by abdominal obesity, high blood pressure, high triglycerides (TRIG), low high-density lipoprotein cholesterol (HDL-C), and elevated fasting blood glucose (FG) (6). Moreover, each component of MetS is independently and individually associated with an increased risk of CV events and mortality (7–10). Several studies have shown that FG is strongly associated with adverse outcomes in patients with ACS, regardless of the presence of diabetes (11–13), and a low level of HDL-C is generally regarded as an independent CV risk factor (14).

In recent years, an increasing number of studies have investigated the association between biochemical biomarkers and adverse outcomes in patients with CAD, such as the triglyceride/HDL-C ratio (15) and triglyceride-glucose index (16). In several clinical scenarios, these markers are crucial for establishing a diagnosis, determining risk, and guiding therapy. As a comprehensive indicator, the synthesis of FG and HDL-C, i.e., the FG/HDL-C ratio, has seldomly been investigated. To the best of our knowledge, the association between the FG/HDL-C ratio and major adverse CV events (MACEs) and CV death in patients with ACS has not been established. Therefore, we analyzed 11,284 patients with ACS and sought to determine the association between the FG/HDL-C ratio and MACEs and CV death and discussed the effect of the FG/HDL-C ratio on MACEs and CV death in patients with ACS.

## Methods

### Study population

This was a post hoc analysis of data from the Acute Coronary Syndrome Quality Improvement in Kerala (ACS-QUIK) study (we obtained a limited dataset from the Biologic Specimen and Data Repository Information Coordinating Center, National Heart, Lung and Blood Institute, U.S. Department of Health & Human Services). The protocol and results of the ACS-QUIK study have been described and published previously (17, 18). In brief, the ACS-QUIK study was a large, pragmatic, cluster-randomized, stepped-wedge clinical trial assessing the implementation and effect of a locally developed quality improvement toolkit on 30-day MACEs in patients admitted with ACS in Kerala, India. The quality improvement toolkit consisted of audit and feedback, checklists, patient education materials, and linkage to emergency cardiovascular care and quality improvement training. From November 2014 to December 2017, the trial recruited 22,557 volunteers from 63 hospitals; of these, 21,374 were eligible, and 21,079 participants had complete outcome data. However, after adjusting for cluster and temporal trends, compared with usual care, the implementation of the quality improvement toolkit did not reduce the 30-day MACEs rates. After excluding 10,090 patients without baseline FG, HDL-C, or outcome data, we analyzed 11,284 patients in this study.

### Variables and definitions

The variables we used were as follows: cohort, intervention, sex, age, heart rate, weight, systolic blood pressure (SBP), hemoglobin, creatine kinase isoenzymes in the heart (CK-MB), troponin, serum creatinine

(sCr), HDL-C, low-density lipoprotein cholesterol (LDL-C), TRIG, FG, smoking or tobacco, hypertension, peripheral arterial disease (PAD), prior transient ischemic attack (TIA) or stroke, diabetes, ST-segment elevation myocardial infarction (STEMI), heart failure, cardiac shock, cardiac arrest, Killip class, left ventricular ejection fraction (LVEF) category (1: <40%; 2: ≥40%; 3: unknown or not assessed), minutes from symptom onset to arrival, minutes from door to balloon, angiography, percutaneous coronary intervention (PCI), coronary artery bypass graft surgery (CABG), aspirin, clopidogrel, ticagrelor, beta-blocker, warfarin, angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), statin, MACEs, and CV death. The baseline FG and HDL-C levels were defined as the FG and HDL-C levels at the first medical contact. "Intervention" was defined as the use of the quality improvement toolkit. The primary endpoint was 30-day MACEs, defined as death, reinfarction (defined by the third universal definition of myocardial infarction (19)), stroke, or major bleeding. The secondary endpoint was 30-day CV death. "30-day" was defined from the admission to post-discharge 30-days.

## Statistical analysis

All statistical analyses were performed using the statistical software packages R (The R Foundation, Vienna, Austria; <http://www.R-project.org>) and EmpowerStats (X&Y Solutions, Inc., Boston, MA; <http://www.empowerstats.com>). Continuous variables were expressed as mean and standard deviation (SD) or median with interquartile range, depending on whether the data were normally distributed (assessed using normal quantile-quantile [Q-Q] plots and the Lilliefors [Kolmogorov-Smirnov] normality test). Categorical variables were reported as frequencies with percentages. To determine statistical differences between variables, a one-way analysis of variance or the Kruskal-Wallis H test was used for continuous variables (depending on the type of data distribution), and chi-square tests were used for categorical variables. We used multiple logistic regression models to evaluate the association between the FG/HDL-C ratio and MACEs and CV death, including non-adjusted, minor-adjusted, and fully adjusted models. We selected confounders on the basis of their clinical implications, statistically significant differences in the univariable analysis (Supplement Tables 1 and 2), and their change in effect estimate of more than 10%. Both non-adjusted and multivariate-adjusted models were applied. Meanwhile, we used the FG/HDL-C ratio as either a continuous or categorical variable to evaluate the relationship; when the FG/HDL-C ratio was treated as a categorical variable, the first quartile was used as the reference. The interaction and stratified analyses were conducted according to sex, age, heart rate, SBP, smoking or tobacco, hypertension, PAD, prior TIA or stroke, diabetes, STEMI, heart failure, cardiac shock, cardiac arrest, Killip class, LVEF category, angiography, PCI, and CABG. If the equivalent degrees of freedom were >1, a nonlinear relationship was observed. When a non-linear relationship was determined, we used the generalized additive model (GAM) to evaluate the non-linear relationship between the FG/HDL-C ratio and 30-day endpoints. We used a two-piecewise linear regression model to calculate the threshold effect of the relationships between the FG/HDL-C ratio and 30-day endpoints. The inflection point was calculated automatically by the recursive method using the maximum-likelihood model. Different regression coefficients were found on the left and right sides of the inflection point. Finally, we used the logarithmic likelihood ratio test to evaluate whether one-line linear regression models or two-piecewise linear regression models are more appropriate for describing the data.

Table 1  
Baseline characteristics of participants.

Characteristic	Q1 (n=2823)	Q2 (n=2821)	Q3 (n=2830)	Q4 (n=2810)	P-value
FG/HDL-C ratio	1.88 ± 0.33	2.78 ± 0.25	3.80 ± 0.37	6.52 ± 2.07	<0.001
Intervention	1222 (43.29%)	1436 (50.90%)	1429 (50.49%)	1405 (50.00%)	<0.001
Sex					0.006
Female	715 (25.33%)	684 (24.25%)	614 (21.70%)	703 (25.02%)	
Male	2108 (74.67%)	2137 (75.75%)	2216 (78.30%)	2107 (74.98%)	
Age (years)	60.64 ± 12.63	60.40 ± 12.22	59.42 ± 11.81	59.97 ± 11.50	<0.001
Heart rate (BPM)	78.71 ± 18.21	79.68 ± 19.40	80.10 ± 19.08	82.93 ± 20.46	<0.001
Weight (kg)	62.31 ± 9.36	63.13 ± 9.71	64.16 ± 9.77	64.22 ± 9.59	<0.001
SBP (mmHg)	138.49 ± 27.74	141.78 ± 28.71	140.78 ± 29.49	139.85 ± 29.92	<0.001
Hemoglobin (g/dL)	13.17 ± 1.99	13.36 ± 1.97	13.47 ± 1.99	13.18 ± 2.09	<0.001
CK-MB (units/L)	65.77 ± 83.07	71.26 ± 91.22	74.03 ± 93.68	64.66 ± 88.11	0.087
Troponin (ng/mL)	8.80 ± 22.86	10.88 ± 24.20	11.55 ± 26.99	9.33 ± 22.56	0.471
Serum Creatinine (units/L)	1.16 ± 0.54	1.14 ± 0.54	1.17 ± 0.65	1.22 ± 0.74	0.020
HDL-C (mg/dL)	49.53 ± 11.04	42.65 ± 8.48	39.06 ± 8.99	36.09 ± 9.11	<0.001
LDL-C (mg/dL)	125.08 ± 37.83	125.05 ± 40.55	123.17 ± 40.63	118.47 ± 41.81	<0.001
TRIG (mg/dL)	130.37 ± 60.91	129.67 ± 64.97	138.14 ± 71.63	153.52 ± 84.79	<0.001

BPM: beats per minute. SBP: systolic blood pressure. CK-MB: creatine kinase isoenzymes in the heart. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. TRIG: triglycerides. PAD: peripheral arterial disease. TIA: transient ischemic attack. STEMI: ST-segment elevation myocardial infarction. LVEF: left-ventricular ejection fraction. LVEF category: 1: ≤40%; 2: 40–70%; 3: ≥70%; 4 = unknown or not assessed. PCI: percutaneous coronary intervention. CABG: coronary-artery bypass graft surgery. ACEI: angiotensin-converting enzyme inhibitor. ARB: Angiotensin receptor blocker. MACE: major adverse cardiovascular events. CV death: cardiovascular death.

Characteristic	Q1 (n=2823)	Q2 (n=2821)	Q3 (n=2830)	Q4 (n=2810)	P-value
Fasting glucose (mg/dL)	91.78 ± 20.83	118.36 ± 24.42	148.15 ± 36.61	230.90 ± 75.54	<0.001
Smoking or tobacco	1156 (40.95%)	860 (30.49%)	855 (30.21%)	709 (25.23%)	<0.001
Hypertension	1132 (40.10%)	1249 (44.28%)	1397 (49.36%)	1424 (50.68%)	<0.001
PAD	18 (0.64%)	31 (1.10%)	26 (0.92%)	44 (1.57%)	0.006
Prior TIA or stroke	78 (2.76%)	66 (2.34%)	53 (1.87%)	79 (2.81%)	0.079
Diabetes	652 (23.10%)	946 (33.53%)	1556 (54.98%)	2242 (79.79%)	<0.001
STEMI	1751 (62.03%)	1884 (66.78%)	1892 (66.86%)	1841 (65.52%)	<0.001
Heart failure	181 (6.41%)	261 (9.25%)	289 (10.21%)	309 (11.00%)	<0.001
Cardiac shock	49 (1.74%)	38 (1.35%)	60 (2.12%)	95 (3.38%)	<0.001
Cardiac arrest	26 (0.92%)	21 (0.74%)	36 (1.27%)	38 (1.35%)	0.085
Killip class					<0.001
I	2499 (88.52%)	2456 (87.06%)	2429 (85.83%)	2324 (82.70%)	
II	86 (3.05%)	157 (5.57%)	164 (5.80%)	184 (6.55%)	
III	155 (5.49%)	168 (5.96%)	190 (6.71%)	244 (8.68%)	
IV	83 (2.94%)	40 (1.42%)	47 (1.66%)	58 (2.06%)	
LVEF category					<0.001
1	281 (9.95%)	363 (12.87%)	408 (14.42%)	505 (17.97%)	
2	2083 (73.79%)	1996 (70.76%)	1971 (69.65%)	1908 (67.90%)	
3	142 (5.03%)	166 (5.88%)	191 (6.75%)	137 (4.88%)	
4	317 (11.23%)	296 (10.49%)	260 (9.19%)	260 (9.25%)	

BPM: beats per minute. SBP: systolic blood pressure. CK-MB: creatine kinase isoenzymes in the heart. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. TRIG: triglycerides. PAD: peripheral arterial disease. TIA: transient ischemic attack. STEMI: ST-segment elevation myocardial infarction. LVEF: left-ventricular ejection fraction. LVEF category: 1: ≤40%; 2: 40–70%; 3: ≥70%; 4 = unknown or not assessed. PCI: percutaneous coronary intervention. CABG: coronary-artery bypass graft surgery. ACEI: angiotensin-converting enzyme inhibitor. ARB: Angiotensin receptor blocker. MACE: major adverse cardiovascular events. CV death: cardiovascular death.

Characteristic	Q1 (n=2823)	Q2 (n=2821)	Q3 (n=2830)	Q4 (n=2810)	P-value
Symptom onset to arrival (min)	809.61 ± 1263.34	763.32 ± 1269.04	773.15 ± 1272.50	783.14 ± 1292.02	0.573
Door to balloon (min)	538.33 ± 1421.01	483.20 ± 1204.73	510.32 ± 1513.07	511.91 ± 1489.49	0.832
Angiography	1313 (46.51%)	1942 (68.84%)	2067 (73.04%)	1989 (70.78%)	<0.001
PCI	1000 (35.42%)	1615 (57.25%)	1735 (61.31%)	1640 (58.36%)	<0.001
CABG	8 (0.28%)	20 (0.71%)	15 (0.53%)	14 (0.50%)	0.162
Aspirin	2350 (97.31%)	2595 (97.34%)	2623 (97.73%)	2529 (97.49%)	0.060
Clopidogrel	2046 (84.72%)	2120 (79.52%)	2072 (77.20%)	2042 (78.72%)	<0.001
Ticagrelor	223 (9.23%)	347 (13.02%)	378 (14.08%)	344 (13.26%)	<0.001
Beta blocker	1392 (57.64%)	1600 (60.02%)	1703 (63.45%)	1607 (61.95%)	<0.001
Warfarin	30 (1.24%)	48 (1.80%)	66 (2.46%)	50 (1.93%)	0.059
ACEI	769 (31.84%)	963 (36.12%)	962 (35.84%)	873 (33.65%)	0.001
ARB	202 (8.36%)	233 (8.74%)	240 (8.94%)	243 (9.37%)	0.018
Statin	2340 (96.89%)	2557 (95.91%)	2583 (96.24%)	2513 (96.88%)	0.222
MACEs	111 (3.93%)	103 (3.65%)	100 (3.53%)	154 (5.48%)	<0.001
CV death	75 (2.66%)	71 (2.52%)	62 (2.19%)	115 (4.09%)	<0.001

BPM: beats per minute. SBP: systolic blood pressure. CK-MB: creatine kinase isoenzymes in the heart. HDL-C: high-density lipoprotein cholesterol. LDL-C: low-density lipoprotein cholesterol. TRIG: triglycerides. PAD: peripheral arterial disease. TIA: transient ischemic attack. STEMI: ST-segment elevation myocardial infarction. LVEF: left-ventricular ejection fraction. LVEF category: 1: ≤40%; 2: 40–70%; 3: ≥70%; 4 = unknown or not assessed. PCI: percutaneous coronary intervention. CABG: coronary-artery bypass graft surgery. ACEI: angiotensin-converting enzyme inhibitor. ARB: Angiotensin receptor blocker. MACE: major adverse cardiovascular events. CV death: cardiovascular death.

## Results

### Baseline characteristics of participants

All patients were subdivided into four quartiles according to the FG/HDL-C ratio levels. Table 1 shows the baseline characteristics of the study population according to the FG/HDL-C ratio quartiles. Briefly, a total

of 11,284 patients (8,568 male patients and 2,716 female patients) were available for the final baseline analysis. Their age was  $60.11 \pm 12.05$  years; 5,202 patients (46.10%) had a history of hypertension, and 5,396 (47.82%) had a history of diabetes. The FG/HDL-C ratio was  $3.75 \pm 2.05$ . There were statistically significant differences ( $P < 0.05$ ) among the four quartiles in terms of intervention, sex, age, heart rate, weight, SBP, hemoglobin, sCr, HDL-C, LDL-C, TRIG, FG, smoking or tobacco, hypertension, PAD, diabetes, STEMI, heart failure, cardiac shock, Killip class, LVEF category, angiography, PCI, and the use of medications including clopidogrel, ticagrelor, beta-blocker, ACEI, and ARB. No statistically significant differences were found for the other indicators. Patients with FG/HDL-C ratio levels in the highest quartile had higher levels of sCr and FG and lower levels of HDL-C and LDL-C, had a higher incidence of hypertension, PAD, diabetes, heart failure, and cardiac shock, and fewer of them smoked.

## Relationship between FG/HDL-C ratio and adverse outcomes

The multivariable stepwise analysis of the three models (non-adjusted model, minor-adjusted model, and fully adjusted model) is shown in Tables 2. The FG/HDL-C ratio was significantly associated with an increased risk of MACEs in patients in the highest quartile (non-adjusted model, odds ratio [OR]: 1.42; 95% confidence interval [CI], [1.10, 1.82];  $P < 0.01$ ) (minor-adjusted model, OR: 1.57; 95% CI, [1.21, 2.03];  $P < 0.01$ ) (fully adjusted model, OR: 1.49; 95% CI, [1.11, 1.99];  $P < 0.01$ ). Regarding CV death, patients in the highest quartile had the highest risk (non-adjusted model, OR: 1.56; 95% CI, [1.16, 2.10];  $P < 0.01$ ) (minor-adjusted model, OR: 1.77; 95% CI, [1.30, 2.39];  $P < 0.01$ ) (fully adjusted model, OR: 1.69; 95% CI, [1.01, 1.41];  $P = 0.04$ ) compared with those in the lowest quartile. When we used the FG/HDL-C ratio as a continuous covariate, in the non-adjusted model, the risk of MACEs and CV death increased as the FG/HDL-C ratio increased (MACEs, OR: 1.09; 95% CI, [1.05, 1.13];  $P < 0.01$ ) (CV death, OR: 1.11; 95% CI, [1.07, 1.16];  $P < 0.01$ ). In the minor-adjusted model, there was no significant change in the results after adjustment (MACEs, OR: 1.10; 95% CI, [1.06, 1.15];  $P < 0.01$ ) (CV death, OR: 1.13; 95% CI, [1.08, 1.18];  $P < 0.01$ ). In the fully adjusted model, fully adjusting for confounders also did not change the trend (MACEs, OR: 1.09; 95% CI, [1.04, 1.14];  $P < 0.01$ ) (CV death, OR: 1.11; 95% CI, [1.04, 1.19];  $P < 0.01$ ).

**Table 2.** Relationship between the FG/HDL-C ratio and short-term outcomes in different models.



<b>MACEs</b>			
Exposure	Non-adjusted	Minor-adjusted	Fully adjusted
FG/HDL-C ratio	1.09 (1.05, 1.13), P < 0.01	1.10 (1.06, 1.15), P < 0.01	1.09 (1.04, 1.14), P < 0.01
FG/HDL-C ratio grouping			
Q1	Ref	Ref	Ref
Q2	0.93 (0.70, 1.22), P = 0.58	0.95 (0.72, 1.26), P = 0.75	0.98 (0.73, 1.30), P = 0.88
Q3	0.89 (0.68, 1.18), P = 0.43	1.00 (0.76, 1.33), P = 0.98	1.03 (0.76, 1.38), P = 0.86
Q4	1.42 (1.10, 1.82), P < 0.01	1.57 (1.21, 2.03), P < 0.01	1.49 (1.11, 1.99), P < 0.01
<b>CV death</b>			
Exposure	Non-adjusted	Minor-adjusted	Fully adjusted
FG/HDL-C ratio	1.11 (1.07, 1.16), P < 0.01	1.13 (1.08, 1.18), P < 0.01	1.11 (1.04, 1.19), P < 0.01
FG/HDL-C ratio grouping			
Q1	Ref	Ref	Ref
Q2	0.95 (0.68, 1.31), P = 0.74	0.98 (0.70, 1.38), P = 0.92	1.01 (0.59, 1.71), P = 0.98
Q3	0.82 (0.58, 1.15), P = 0.26	0.94 (0.66, 1.33), P = 0.71	0.83 (0.48, 1.46), P = 0.53
Q4	1.56 (1.16, 2.10), P < 0.01	1.77 (1.30, 2.39), P < 0.01	1.69 (1.01, 1.41), P = 0.04

Co-linearity analysis showed that FG, cardiac arrest, PCI, CABG and FG/HDL-C ratio had high co-linearity. Therefore, FG, cardiac arrest, PCI, and CABG weren't included in multivariate model.

For MACEs, in the non-adjusted model, we did not adjust other covariates. In the minor-model, we adjusted for cohort, intervention, age, and sex. In the fully model, we adjusted for cohort, intervention, age, sex, heart rate, weight, SBP, hemoglobin, TRIG, smoking or tobacco, hypertension, prior TIA or stroke, diabetes, heart failure, cardiac shock, Killip class, LVEF category.

For CV death, in the non-adjusted model, we did not adjust other covariates. In the minor-model, we adjusted for cohort, intervention, age, and sex. In the fully model, we adjusted for cohort, intervention, age,

sex, weight, heart rate, troponin, TRIG, smoking or tobacco, hypertension, diabetes, heart failure, cardiac shock, Killip class, LVEF category, symptom onset to arrival.

## Analyses of non-linear relationship

The GAM suggested non-linear relationships between the FG/HDL-C ratio and MACEs and CV death according to the equivalent degrees of freedom of GAM which were 1.03 for MACEs and 1.14 for CV death (Figure 1 (A) and (B)). We used two-piecewise linear regression models to characterize the relationship (Table 3). In addition, we identified 3.02 and 3.00 as the threshold values for MACEs and CV death, respectively. Below these threshold values, the FG/HDL-C ratio was not associated with MACEs or CV death. However, above these threshold values, the FG/HDL-C ratio increased, and the risk of MACEs and CV death increased (MACEs, OR: 1.12; 95% CI, [1.07, 1.17];  $P < 0.01$ ; CV death, OR: 1.15; 95% CI, [1.09, 1.20];  $P < 0.01$ ).

Table 3  
Results of two-piecewise linear-regression model.

Outcome: MACEs		Outcome: CV death	
Exposure: FG/HDL-C ratio		Exposure: FG/HDL-C ratio	
One linear-regression model	1.09 (1.05, 1.13), $P < 0.01$	One linear-regression model	1.11 (1.07, 1.16), $P < 0.01$
Inflection point (K)	3.02	Inflection point (K)	3.00
<K Effect size $\beta$ (95%CI)	0.88 (0.72, 1.07), $P = 0.20$	<K Effect size $\beta$ (95%CI)	0.85 (0.67, 1.08), $P = 0.20$
>K Effect size $\beta$ (95%CI)	1.12 (1.07, 1.17), $P < 0.01$	>K Effect size $\beta$ (95%CI)	1.15 (1.09, 1.20), $P < 0.01$
P for Log likelihood ratio test	0.03	P for Log likelihood ratio test	0.03
<b>(A) (B)</b>			
(A) MACEs: major adverse cardiovascular events and (B) CV death: cardiovascular death. The two-piecewise linear regression model was used to calculate the threshold effect.			

## Subgroup analysis and interaction test

The results of the stratified analysis are illustrated in Supplementary Figures 1 and 2. For MACEs, the significant variable in the interaction test was CABG ( $P < 0.01$ ). The OR without CABG was less than that with CABG (1.09 vs. 2.59), and the 95% CIs did not overlap (1.04, 1.13;  $P < 0.01$  vs. 1.17, 5.72;  $P = 0.02$ ). For CV death, the significant variable in the interaction test was age ( $P < 0.05$ ). The ORs of patients aged  $\geq 75$  years were less than those of patients aged  $< 75$  years (1.04 vs. 1.15); however, the 95% CIs

overlapped (1.10, 1.21;  $P < 0.01$  vs. 0.95, 1.14;  $P = 0.39$ ). A high FG/HDL-C ratio indicated a higher risk of MACEs in patients with CABG than in patients without CABG (Figure 2 (C)). In those aged  $<75$  years, a high FG/HDL-C ratio indicated a higher risk of CV death than in patients aged  $\geq 75$  years (Figure 2 (D)).

## Discussion

We investigated the association between the FG/HDL-C ratio and MACEs and CV death in patients undergoing ACS. Our study demonstrated for the first time that the incidence of MACEs and CV death within 30 days after admission was higher among patients with ACS with FG/HDL-C ratios in the highest quartile. For MACEs, the inflection point was 3.02; when the FG/HDL-C ratio was  $>3.02$ , the incidence of MACEs increased by 12% for every increase of 1 in the FG/HDL-C ratio. For CV death, the inflection point was 3.00; when the FG/HDL-C ratio was  $>3.00$ , the incidence of CV death increased by 15% for every increase of 1 in the FG/HDL-C ratio. Therefore, a higher FG/HDL-C ratio was associated with a higher incidence of MACEs and CV death in patients with ACS.

During the pathophysiological process leading to CADs, glycoxidation products from hyperglycemia result in superoxide overproduction in arterial endothelial cells leading to inflammation and impaired endothelial function (20). Meanwhile, when arterial endothelial cells encounter dyslipidemia, adhesion molecule expression is augmented, and the adhesion of blood leukocytes to the inner surface of the arterial wall is promoted (21). Hyperglycemia and low HDL levels are known risk factors that are significantly associated with adverse outcomes in patients with ACS. Farhan *et al.* reported that among patients with high-risk non-STEMI ACS, for every 1 mg/dL increase in FG, the hazard ratio (HR) for 1-year death increased by 53% (22). Similar findings were reported by other investigators; Ramos *et al.* demonstrated that FG is associated with MACEs in older and younger patient groups ( $<65$  years and  $\geq 65$  years) (23). However, the number of patients included in the study was relatively small, only 580 patients. Statin, a lipid-lowering drug, is widely prescribed for the treatment of CVD. Statin treatment slightly increases serum HDL-C levels; however, in some clinical settings, there is a paradoxical decrease in HDL-C levels. In a previous study, the HR for MACEs increased by 56% for every 1 mg/dL reduction in HDL-C in patients initiated on statin treatment (24). Similarly, Hirayama *et al.* demonstrated that compared with LDL-C levels, HDL-C levels were more strongly associated with the incidence of MACEs, especially in patients with stable angina pectoris (25). The follow-up in the trial of Hirayama *et al.* was up to 7 years. Overall, these findings extend the previously reported findings from other investigators. As a composite indicator, the FG/HDL-C ratio consists of two major indicators: both FG and HDL-C are associated with poor prognosis in patients with ACS. However, whether the combined effect of the two indicators is greater than a single indicator remained unclear. Therefore, we assessed the association between the FG/HDL-C ratio and 30-day MACEs and 30-day CV death.

In recent years, several novel biomarkers have been reported, including microRNAs (26) and long non-coding ribonucleic acids (27). However, measuring these biomarkers is expensive, time-consuming, and complicated. Therefore, a number of limitations should be considered when searching for better biomarkers. In intensive biomarker research studies, some biomarkers showed statistically significant

results for adverse outcomes in patients with CAD, such as red blood cell distribution width (28), gamma-glutamyl transferase-to-platelet ratio (29), mean platelet volume (30), monocyte-to-HDL ratio (31), triglyceride/HDL-C ratio (15), and triglyceride-glucose index (16). These biomarkers are more accessible, convenient, and economical and can serve to supplement traditional prognostic indicators and provide new information for clinical assessment and treatment; however, their sensitivity and specificity vary.

Recently, the relationship between the FG/HDL-C ratio and clinical adverse outcomes was studied in patients without diabetes after PCI (32). The findings suggested that the incidence of all-cause mortality increased by 28.4% in patients with a higher FG/HDL-C ratio (HR: 1.284; 95% CI, [1.010, 1.631];  $P < 0.05$ ). However, few studies have been conducted on the FG/HDL-C ratio in other populations. Therefore, in our study, we focused on the ACS population, regardless of whether they had diabetes. Our multivariate logistic regression analysis showed that an increased FG/HDL-C ratio was associated with MACEs and CV death, which is in agreement with the findings of Guo *et al.* (32). However, it is worth mentioning that further subgroup analyses in our study suggested that the ORs of patients with diabetes were less than those of patients with diabetes for MACEs, and the ORs of patients with diabetes were higher than those of patients with diabetes for CV death (MACEs, 1.08 vs 1.09; CV death, 1.11 vs. 1.10), although the interaction did not reach statistical significance.

In the present study, we analyzed more than 10,000 patients with ACS in India. All patients were divided into four groups according to their FG/HDL-C ratio levels. In the baseline characteristic analysis, several baseline characteristics were significantly different between the four groups, and there may have been some unmeasured differences between the four groups. Considering the effect of these confounders, we performed multivariate logistic regression analysis to reduce the effect of the confounders; however, the ORs were not substantially altered. After the subgroup analysis, our data showed that the increased risk of MACEs was more pronounced in patients undergoing CABG, and the increased risk of CV death was more pronounced in patients aged  $<75$  years. Based on these findings, our study highlights some aspects of the management of patients with ACS, and we should pay close attention to patients with ACS undergoing CABG and aged  $<75$  years with a high FG/HDL-C ratio.

Our study had several limitations. First, to minimize the effect of confounders, we adjusted for many variables as completely as possible; however, because of the incompleteness of the original data, we cannot ensure that all confounding variables were fully adjusted. Second, some patients did not undergo coronary angiography or PCI because of patients' refusal or poor clinical condition, resulting in a lower perfusion rate after primary angioplasty which may have impacted our results to a certain extent. Third, because we used data from hospitals in Kerala, India, the external validity of our results is limited. Moreover, the follow-up time was only 30 days, and a longer follow-up time might have affected the results. Finally, the key limitation is that a large number of patients, approximately the 50%, was excluded from the present study due to missing data.

## Conclusions

In conclusion, our study demonstrated that the FG/HDL-C ratio may be an accessible, convenient, and economical biomarker of short-term outcomes in patients with ACS and could be used to guide their clinical management.

## Abbreviations

CAD

coronary artery disease

FG

fasting blood glucose

HDL-C

high-density lipoprotein cholesterol

ACS

acute coronary syndrome

MACEs

major adverse cardiovascular events

CV

cardiovascular

ACS-QUIK

acute coronary syndrome quality improvement in Kerala

GAM

generalized additive model

MetS

metabolic syndrome

TRIG

triglycerides

SBP

systolic blood pressure

CK-MB

creatine kinase isoenzymes in the heart

sCr

serum creatinine

LDL-C

low-density lipoprotein cholesterol

PAD

peripheral arterial disease

TIA

transient ischemic attack

STEMI

ST-segment elevation myocardial infarction

LVEF

left ventricular ejection fraction

PCI

percutaneous coronary intervention

CABG

coronary artery bypass graft surgery

ACEI

angiotensin-converting enzyme inhibitor

ARB

angiotensin receptor blocker

SD

standard deviation

## **Declarations**

### **Ethics approval and consent to participate**

No applicable

### **Consent for publication**

No applicable

### **Availability of data and materials**

Data are available from the Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).

### **Competing interests**

The authors have no conflict of interest to declare.

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### **Author contributions**

Xinqun Hu and Simin Deng designed the study and provided methodological expertise. Simin Deng drafted the manuscript. Simin Deng, Zhaojun Wang, Yifeng Zhang, and Ying Xin drafted the tables and figures and performed statistical analysis. Cheng Zeng revised the manuscript. All authors have read and approved the final manuscript.

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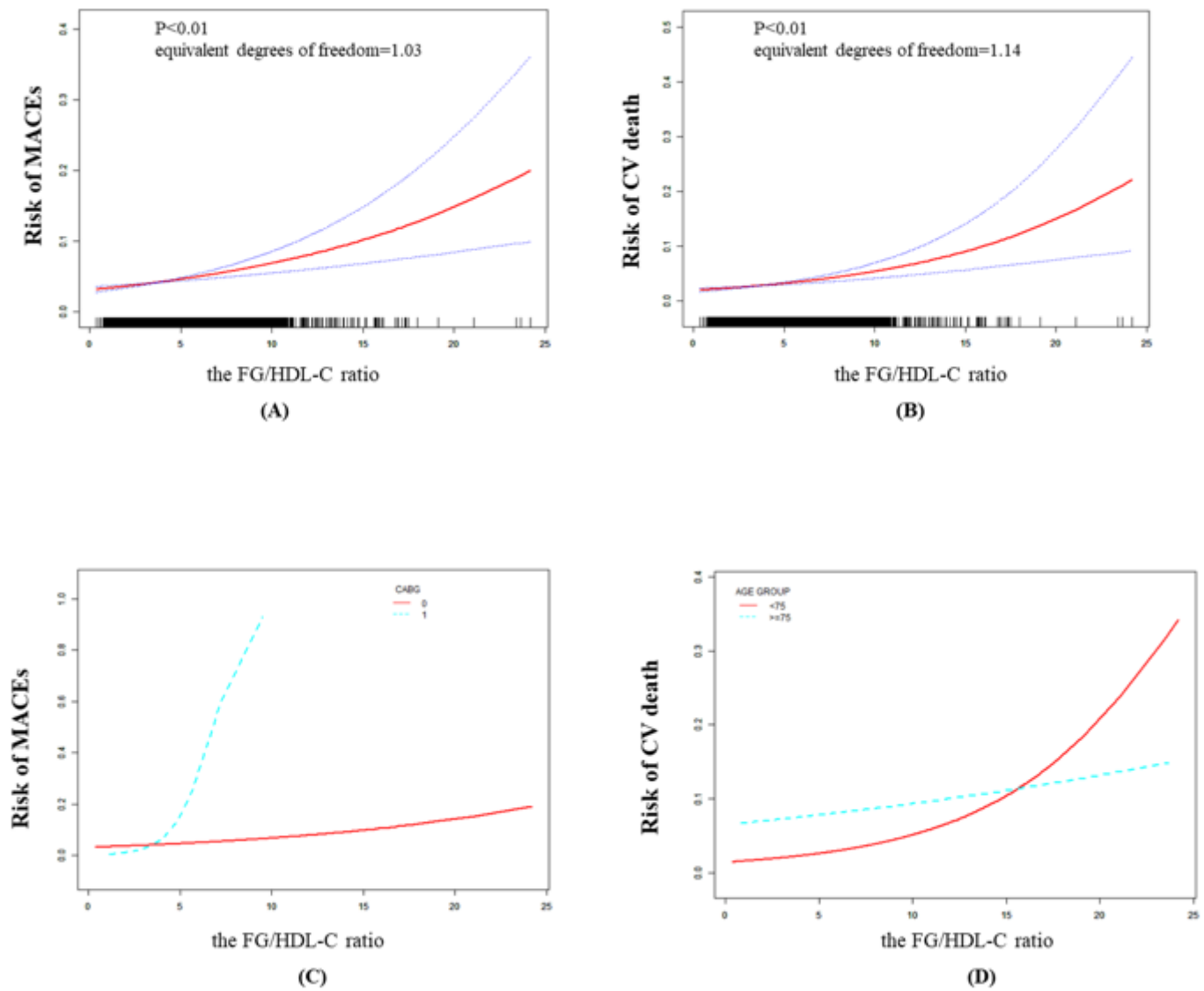
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## Figures



**Figure 1**

Relationship between the FG/HDL-C ratio and MACEs (A), and CV death (B); Relationship between the FG/HDL-C ratio and MACEs grouped by CABG (C), and CV death grouped by age (D). The red line is the trend line, and the blue line is the 95% confidence interval. The denser the vertical lines, the greater the number of patients in the area. CABG 0: without CABG, CABG 1: with CABG.

## Supplementary Files

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