Increased glycoprotein acetylation is associated with high cardiac event rates: Analysis using coronary computed tomography angiography

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Abstract

Objective: Glycoprotein acetylation (GlycA), an emerging inflammatory biomarker, has been used as an indicator of cardiovascular disease. Our research aimed to evaluate the correlation between GlycA and coronary artery disease (CAD) using coronary computed tomography angiography (CCTA).

Methods: In the present study, a total of 342 patients were enrolled, and each of them underwent CCTA. The correlation between GlycA and major adverse cardiac events (MACE) was detected via Cox's proportional hazards models. Based on differences in the GlycA level, patients were categorized into three groups (T1, T2, and T3).

Results: Compared with the group with the lowest GlycA level (T1), the group with the highest GlycA level (T3) exhibited stronger atherosclerotic pressure involving the extent of atherosclerotic plaque and risk of obstructive CAD. In addition, the patients in the T3 group had a greater chance of experiencing MACE and higher all-cause mortality than those in the T1 group. Among patients without CAD who underwent CCTA, those with high GlycA levels experienced elevated atherosclerotic stress and heightened risk of MACE compared with those with low GlycA levels.

Conclusion: These results suggest that serum GlycA is significantly associated with the long-term clinical results of patients with no known CAD undergoing CCTA. The risks of death and experiencing MACE increase among patients with high GlycA levels. *(Anatol J Cardiol 2018; 20: 152-8)*

Keywords: glycoprotein acetylation, coronary artery disease, coronary computed tomography angiography, plaque

Introduction

Glycoprotein acetylation (GlycA), a complex, heterogeneous, nuclear magnetic resonance signal originating from mobile glycan residues on plasma glycoproteins, is a novel composite biomarker of systemic inflammation (1-3). Recent studies have demonstrated GlycA to be a strong predictor of incident type 2 diabetes mellitus, long-term severe infection risk, and overall mortality (4). Moreover, GlycA has shown promise as a marker of disease activities, treatment response, and coronary artery disease (CAD) among patients with inflammatory disorders, such as rheumatoid arthritis and systemic lupus erythematosus (5-7).

Coronary computed tomography angiography (CCTA) has been utilized as a nontraumatic method to determine the existence, type, stage, and severity of CAD (8, 9). Many prognostic studies have demonstrated that the severity of coronary artery atherosclerosis revealed via CCTA effectively predicts later cardiac events in patients with a variety of conditions.

Inflammation plays a key role in the onset and development of atherosclerosis, leading to cardiovascular disease (CVD) events (10, 11). The effect of these biological inflammatory markers, such as GlycA, in terms of disease prediction has been observed in patients with existing CAD and in normal patients in the control group (12). Numerous studies have supported the impact of chronic inflammation in the development process of atherosclerosis (13, 14). Furthermore, some studies have shown that increasing GlycA or other inflammatory factors can predict a number of fatal chronic diseases in elderly patients and can trigger and maintain systemic inflammation (6, 15). To date, whether GlycA is an effective indicator of car-

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diac events in patients with no known CAD undergoing CCTA remains unclear. Therefore, this study aimed to investigate whether serum GlycA is an effective biological indicator in the prediction of future cardiovascular events in patients with no known CAD undergoing CCTA.

Methods

Study population

A total of 489 observation patients were recruited to the study, and all patients underwent CCTA assessment. In the present study, only those patients with available serum GlycA records were enrolled. The patients who had CAD, malignancy, and inflammatory disease and those who lacked serum GlycA data were not included. Consequently, a total of 342 patients were enrolled. The reviewing committee approved the procedure of experiments, and all enrolled patients provided written informed consent. The patients were categorized into three groups based on their serum GlycA level (<359, 360-456, and >457 μmol/L). The demographic data and risk factors of CAD, e.g., the addiction to cigarettes, high blood pressure, diabetes, blood lipid abnormality, and family medical history, were obtained before CCTA assessment via face-to-face interview with patients by a medical doctor with or without standardized onsite questionnaires. High blood pressure was determined via a self-statement, administration history of antihypertensive drugs, or a tested blood pressure of 140/90 mm Hg. Diabetes was determined as having a reading of hemoglobin A1c of >6.5%. The standard of blood lipid abnormality was measured as low-density lipoprotein cholesterol >140 mg/dL and high-density lipoprotein cholesterol <40 mg/dL.

Major adverse cardiac events assessment

Major adverse cardiac events (MACE) was the primary outcome, comprising target vascular reconstruction (TVR), all-cause death, and acute coronary syndrome (ACS). Follow-ups were conducted via medical chart assessment, telephone contact, direct interview, and mailed questionnaires. Data regarding death were gathered from detailed medical records both from our hospital and others. Patients were then divided into two groups based on different causes of death, all-cause death or cardiovascular death (e.g., stroke, CAD, and sudden cardiac death).

Imaging assessment

All scanning results from computed tomography (CT) scanners (64 slices or above) were analyzed by two different radiologists who were blinded to the clinical information. The decision to perform CCTA assessment was reached via consensus. An adjusted coronary tree model developed by the American Heart Association was applied for disease detection. Plaque characteristics on CCTA, including plaque site, severity, and features, were evaluated by level 3 equivalent readers according to guidelines. Coronary artery plaques were recognized as a hyperdense or hypodense part that was different from the lumen with a size >1 mm^2. The severity of CAD was categorized into three levels according to the extent of luminal stenosis: none (0%), nonobstructive (<50%), and obstructive (≥50%), which was then subcategorized as 1-vessel disease (VD), 2-VD, and 3-VD. To evaluate the progression of CAD, the segment involvement score (SIS) was used. This score measures the number of coronary artery segments with CAD, which reveals the extent of CAD; SIS was categorized into three groups: 0, 1–5, and >5. According to characteristics, plaques were divided into the following groups: calcified plaques (CAP), noncalcified plaques (NCAP), and mixed calcified plaques (MCAP).

GlycA measurement

NMR spectra were obtained from ethylenediaminetetraacetic acid plasma samples for the NMR LipoProfile test at LipoScience. The NMR Profiler platform comprises a 9.4-T spectrometer with a frequency of 400 MHz ^1H and a fluidic sample delivering system. The GlycA level signal was measured using deconvolution software that employed the linear least square method to align experimental signals with independent spectral parts, involving proteins, lipoproteins, and signals from the resonance of GlycA and NMR. The GlycA levels were measured with those spectra.

Statistical analysis

Normally distributed variables are presented as mean±SD, and the one-way ANOVA test was used for comparison of across teriles. Non-normally distributed variables are expressed as medians with interquartile range, and the Kruskal-Wallis test was used for comparison of the three groups. The correlation between GlycA and the endpoints of time to all-cause death or MACE was evaluated using adapted Cox's proportional hazards models, which was adjusted in terms of age, sex, body mass index, CAD risk factors (high blood pressure, lipid disorder, diabetes, smoking status, and family medical history), obstructive CAD existence, and SIS. The incident rates were analyzed using the log-rank test. MACE or survival curves across tertiles were prepared using multivariate Cox's proportional hazards models after adjusting variables in each GlycA level. Moreover, the severity of coronary stenosis in CAD, categorized as normal, obstructive, and nonobstructive, and the extent (SIS 0, 1–5, >5) were evaluated across tertile groups using Cox's proportional hazard models with adjustments in terms of demographic characteristics, high blood pressure, lipid disorder, diabetes, and family medical history. Schoenfeld residuals were applied to validate underlying assumptions of Cox's proportional hazards models. Both hazard ratio (HR) and 95% confidence interval (CI) were measured in the abovementioned models. $P<0.05$ indicated statistical significance. All statistical evaluations were performed using Stata 12 (StataCorp, College Station, TX, USA).

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Results

Baseline characteristics of patients

Among the 489 patients who were undergoing CCTA, 342 had GlycA data (Fig. 1). Table 1 shows procedural patient characteristics according to GlycA tertile. Multiple variances were found across tertiles. Compared with patients with the lowest GlycA level (T1), those with the highest GlycA level (T3) were more often symptomatic. Furthermore, patients with high GlycA levels were more often smokers and had high levels of high-sensitivity C-reactive protein (hs-CRP) and low-density lipoprotein cholesterol and low levels of high-density lipoprotein cholesterol.

Status and severity of CAD

Table 2 presents the extent and severity of CAD. The severity of CAD was determined via SIS. Compared with patients with the lowest GlycA level, those with the highest GlycA level had a significantly greater extent of coronary artery plaques. In terms of severity, patients with high GlycA levels had a considerably higher prevalence of obstructive CAD than those with low GlycA levels. The types of CAD plaques varied among different cases, as shown in Table 3. In patients with low GlycA levels, the absence of plaques was common. Compared with patients with low GlycA levels, those with high GlycA levels more frequently had CAP, NCAP, and MCAP.

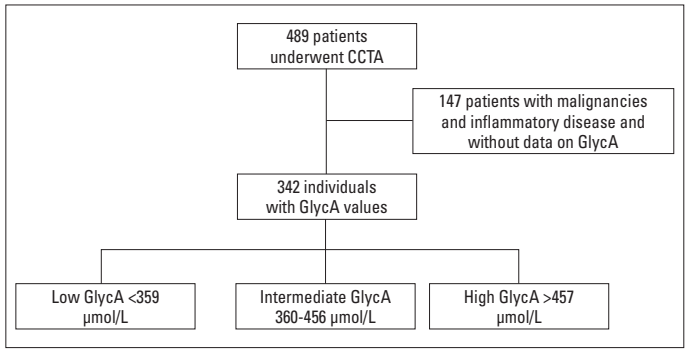

Figure 1. Study flow chart

MACE and all-cause risk of death

At a mean follow-up of 3.9±1.9 years, 41 patients had MACE, accounting for 12.0% of all patients. MACE was observed more often in patients with high GlycA levels than in those with low GlycA levels. We found one patient with TVR and four with ACS in the T1 group, three patients with TVR and seven with ACS in the T2 group, and six patients with TVR and 15 with ACS in the T3 group. In addition, we observed one patient with colon cancer (still alive) and one with non-small cell lung cancer (dead) diagnosed in the T1 group, one patient with pancreatic cancer (dead) diagnosed in the T2 group, and one patient with nasopharyngeal carcinoma and one with colon cancer (both still alive) diagnosed in the T3 group during follow-up. In the unmodulated Cox's model, the incidence rate of MACE and all-cause death correspondingly increased with the GlycA level ($p<0.001$). In a multivariate Cox's proportional hazards model that modulated for age, sex, high blood pressure, blood lipid abnormality, diabetes, family medical history, smoking habit, coronary artery stenosis severity, and SIS, patients with high GlycA

Table 1. Characteristics of study population

	Total (n=342)	Low GlycA (T1) (n=114)	Intermediate GlycA (T2) (n=114)	High GlycA (T3) (n=114)	*P*
GlycA (µmol/L)		≤359	360-456	≥457	<0.001
Male gender	175 (51.2)	58 (50.9)	58 (50.9)	59 (51.8)	0.55
Age (year)	58.3 (10.23)	57.2 (10.55)	58.1 (9.82)	58.9 (10.61)	0.19
Hypertension	180 (52.6)	58 (50.9)	61 (53.5)	61 (53.8)	0.12
Diabetes	62 (18.1)	20 (17.5)	21 (17.5)	21 (18.4)	0.34
Dyslipidemia	212 (62.0)	63 (55.3)	70 (61.4)	79 (69.3)	<0.001
Family history	87 (25.4)	28 (24.6)	29 (25.4)	30 (26.3)	0.28
Current smoker	95 (27.8)	27 (23.7)	30 (26.3)	38 (33.3)	<0.001
BMI (kg/m^2)	25.02 (1.31)	24.99 (1.28)	25.01 (1.14)	25.03 (1.30)	0.32
LDL-C (mg/dL)	127.7 (29.7)	122.8 (28.9)	128.2 (30.2)	134.3 (32.3)	<0.001
HDL-C (mg/dL)	42.8 (11.2)	45.5 (11.7)	42.1 (10.62)	39.2 (9.2)	<0.001
HbA1c (%)	6.56 (1.23)	6.532 (1.17)	6.55 (1.24)	6.58 (1.28)	0.06
hs-CRP (mg/dL)	0.15 (0.03)	0.07 (0.01)	0.16 (0.02)	0.23 (0.02)	<0.001

Values are expressed as n (%) or mean (SD).
BMI - body mass index; GlycA - glycoprotein acetylation; HbA1c - hemoglobin A1c; HDL-C - high-density lipoprotein cholesterol; hs-CRP - high-sensitivity C-creative protein; SD – standard deviation; LDL-C - low-density lipoprotein cholesterol

Table 2. Extent and severity of coronary artery plaque

	Total (n=342)	Low GlycA (T1) (n=114)	Intermediate GlycA (T2) (n=114)	High GlycA (T3) (n=114)	*P*
Vessel disease					
Normal	139 (40.6)	53 (46.5)	47 (41.2)	39 (34.2)	<0.001
Nonobstructive disease	113 (33.0)	42 (36.8)	39 (35.1)	32 (28.1)	<0.001
Obstructive disease	90 (26.3)	19 (16.7)	28 (24.6)	43 (37.7)	<0.001
1-VD	47 (13.7)	12 (10.5)	15 (13.2)	20 (17.5)	<0.001
2-VD	25 (7.3)	4 (3.6)	7 (6.1)	14 (12.3)	<0.001
3-VD	18 (5.3)	3 (2.6)	6 (5.3)	9 (7.9)	<0.001
SIS (Mean±SD)	2.2 ± 2.1	1.8±2.0	2.3±2.1	2.6±2.8	<0.001
SIS 1–5	129 (37.7)	38 (33.3)	42 (36.8)	49 (43.0)	<0.001
SIS >5	54 (15.8)	12 (10.5)	19 (16.7)	23 (20.2)	<0.001

Values are expressed as n (%) or mean (SD).
GlycA - glycoprotein acetylation; SD – standard deviation; SIS - segment involvement score; VD - vessel disease

Table 3. Coronary artery plaque type

Prevalence of any plaque type (%)	Total (n=342)	Low GlycA (T1) (n=114)	Intermediate GlycA (T2) (n=114)	High GlycA (T3) (n=114)	*P*
NCAP	68 (19.9)	19 (16.7)	23 (20.2)	26 (22.8)	<0.001
MCAP	79 (23.1)	20 (17.5)	27 (23.7)	32 (28.1)	<0.001
CAP	92 (26.9)	24 (21.1)	32 (28.1)	36 (31.6)	<0.001

Values are expressed as n (%).
GlycA - glycoprotein acetylation; CAP - calcified plaques; NCAP - non-calcified plaques; MCAP - mixed calcified plaques

Table 4. Cox's proportional hazards model of major adverse cardiac events and all-cause death

	Low GlycA (T1) HR (95% CI)	Intermediate GlycA (T2) HR (95% CI)	High GlycA (T3) HR (95% CI)	*P* HR (95% CI)
Unadjusted Model				
MACE	1.0 (Reference)	1.68 (1.03-2.12)	2.33 (1.82-3.28)	<0.001
All-cause death	1.0 (Reference)	2.12 (1.69-2.87)	3.43 (2.55-4.69)	<0.001
Adjusted Model				
MACE	1.0 (Reference)	1.41 (0.98-1.93)	1.91 (1.34-2.78)	<0.001
All-cause death	1.0 (Reference)	2.22 (1.53-3.09)	3.65 (2.62-5.09)	<0.001

Variables adjusted for were age, body mass index, and diabetes. The covariates were added to this model only if statistically identified as predictors of MACE and all-cause death (P<0.05).
CI - confidence interval; GlycA - glycoprotein acetylation; HR - hazard ratio; MACE - major adverse cardiac events

levels experienced a greater risk of MACE than those with low GlycA levels. Modulated HR improved with rising GlycA levels, even after adjusting for these variables (p<0.001). Moreover, high GlycA levels were associated with all-cause death, as shown in Table 4. The survival rate of MACE clearly increased in tertiles with greater GlycA levels (p<0.001; Fig. 2).

Incidence rate of coronary artery plaque and MACE

Table 5 showed the results of the risk-adjusted Cox proportional-hazards model for MACE by SIS category in GlycA across tertiles. Compared with patients with the lowest GlycA levels with an SIS of 0, patients with the highest GlycA levels with an SIS of 0 (p<0.01, HR 1.5, 95% CI 0.8-2.6) had a greater risk

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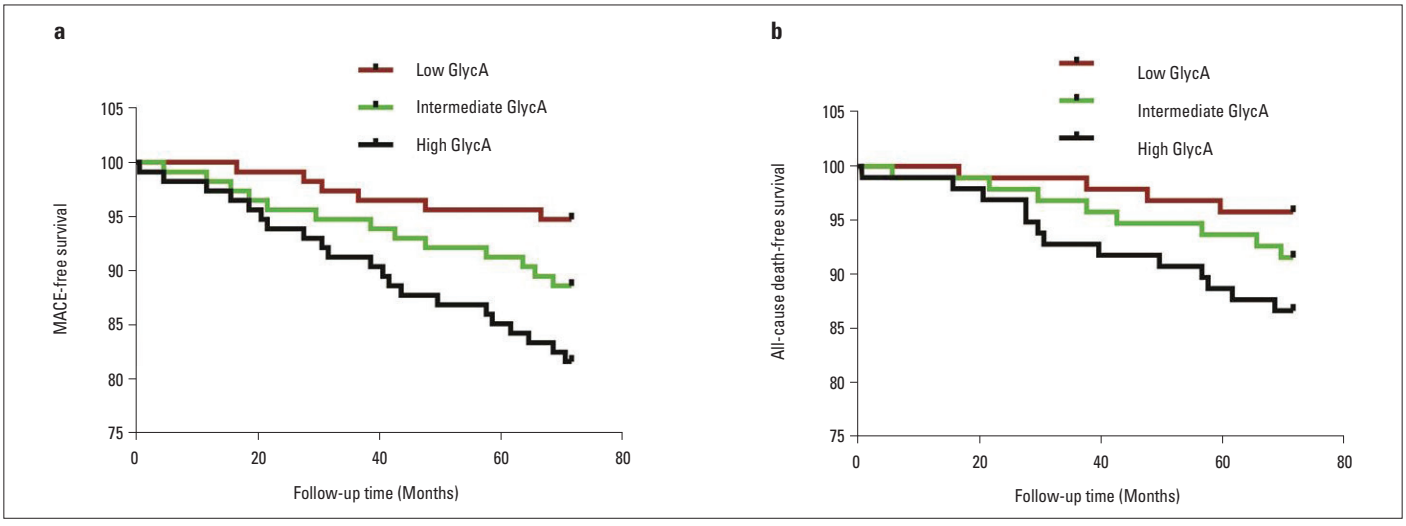

Figure 2. (a) Free survival curves of major adverse cardiac events. (b) Free survival curves of all-cause death
MACE - major adverse cardiac events; GlycA - glycoprotein acetylation

Table 5. Hazard ratio of major adverse cardiac events by coronary artery disease extent

	Low GlycA (T1) HR (95% CI) (n=114)	Intermediate GlycA (T2) HR (95% CI) (n=114)	High GlycA (T3) HR (95% CI) (n=114)
SIS 0	Reference	1.0 (0.4-1.9)	1.5 (0.8-2.6)
SIS 1–5	1.5 (1.0-2.8)	2.2 (1.5-3.2)	3.3 (2.4-4.5)
SIS >5	2.6 (1.7-3.5)	3.2 (2.2-4.3)	4.7 (3.4-6.5)

CI - confidence interval; GlycA - glycoprotein acetylation; HR - hazard ratio; SIS: segment involvement score

Table 6. Hazard ratio of major adverse cardiac events by coronary artery disease severity

	Low GlycA (T1) HR (95% CI) (n=114)	Intermediate GlycA (T2) HR (95% CI) (n=114)	High GlycA (T3) HR (95% CI) (n=114)
Normal	Reference	1.0 (0.3-1.8)	1.8 (0.8-2.7)
Nonobstructive	1.5 (0.8-2.4)	2.3 (1.5-2.9)	3.2 (1.9-4.5)
Obstructive	3.1 (1.7-4.4)	3.7 (2.9-4.8)	5.0 (3.3-6.9)

CI - confidence interval; GlycA - glycoprotein acetylation; HR - hazard ratio

of MACE. In the group with an SIS of 1-5, the incidence rate of MACE was considerably greater than that in the group with an SIS of 0 in GlycA across tertiles. The risk in patients with the highest GlycA levels was significantly greater than that in patients with low GlycA levels (p<0.001, HR 3.3, 95% CI, 2.4-4.5). In the group with an SIS of >5, the incidence rate of MACE was even more elevated in all GlycA across tertiles. In the group with an SIS of 1-5, the incidence rate in patients with the highest GlycA levels was considerably higher than that in patients with lowest GlycA levels (p<0.001, HR 4.7, 95% CI, 3.4-6.5). Table 6 displays the results of the risk-adjusted Cox's model for MACE divided by CAD types (regular, obstructive, and nonobstructive). In patients with nonobstructive CAD with the lowest GlycA levels, the risk of MACE was greater than that of those with normal CCTA (p<0.01, HR 1.5, 95% CI 0.8–2.4). The risk of MACE was considerably greater among patients with the highest GlycA levels (p<0.001, HR 3.7, 95% CI 2.9-4.8). Patients who had obstructive CAD experienced higher MACE ratescompared with lowest GlycA patients with with normal CCTA regardless of GlycA levels (lowest GlycA, p<0.001, HR 3.1, 95% CI 1.7-4.4; highest GlycA, p<0.001, HR 5.0, 95% CI 3.3-6.9).

Discussion

In recent years, the inflammatory hypothesis of atherosclerosis has generated interest in several potential inflammatory biomarkers for CAD (16). These include cytokines (e.g., IL-6, TNF-α, interferon-γ, and monocyte chemoattractant protein-1), endothelial activation mediators (e.g., E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1), and acute-phase reactants (e.g., hs-CRP and GlycA) (17, 18). GlycA, a marker of systemic inflammation, is a promising candidate because it is a validated prognostic biomarker of CAD (6, 7, 19). However, recent evidence has demonstrated that GlycA may not accurately predict CAD in patients with inflammatory conditions (20). GlycA has been detected from the NMR signal that dominantly represents glycosylated acute-phase proteins (21). Glycosylation is the enzymatic chemical modification process where carbohydrate groups are attached to proteins to produce glycoproteins, which is different from the simple binding process of glucose and hemoglobin in patients with diabetes (15, 22). This process plays a significant role in protein folding and stabilization, antigen recognition, cellular signaling, and cell adherence. In the acute-phase reaction, the level of acute-phase glycoproteins changes; in addition, the structures of glycan are altered by glycosidase and glycosyltransferases in circulation. Hence, the assessment of protein glycans through NMR GlycA involves changes in protein and glycan concentrations in inflammatory reactions (5, 23).

Inflammation is an important contributor to atherosclerosis. Elevated GlycA levels, a marker of inflammation, are obviously associated with adverse cardiovascular results. The mechanisms by which this increased risk are associated with elevated plaque vulnerability. Besides the function of inducing immunizing power in plaques, studies have also suggested certain correlations among GlycA, suppression of endothelial nitric oxide synthase, and damaged vascular reactivity. Several previous studies have reported associations between serum GlycA and death (3). Additionally, many previous studies have shown a correlation between GlycA and incidence rate of CVD (6, 7). The report on Women's Health and Aging demonstrated that in women with predominant CVD, patients with a higher plasma GlycA level were four times more likely to die than those in the lowest tertile; however, the same correlation was not confirmed in patients with no known CVD (7, 20, 21). In contrast, serum GlycA levels were positively correlated with the risk of death in patients with CAD (20). GlycA was significantly better associated with all-cause and cardiovascular death than with CRP (2, 24). A recent study discovered that plasma GlycA levels can indicate short- and long-term death in patients with acute heart failure (25). Some other researchers have suggested that improved serum GlycA levels offer important input in the risk evaluation of long-term cardiovascular survival/death among patients with ST-elevation myocardial infarction and can serve as a promising predictive indicator of all-cause and cardiovascular death (20, 25). In addition, our findings also showed that patients with high GlycA levels have a higher incidence of MACE and all-cause death than those with low GlycA levels.

Our study bears certain limitations. First, being an observational study involving a small sample of patients, potential hidden factors could have influenced the results, despite the best efforts of statistical adjustments. The comparatively small number of cases could add to the insufficiency of the significant differences. Accordingly, further large-scale studies are required to verify the findings of the present study. Second, in certain cases, a high GlycA level was associated with infection, but more detailed information about the infection and its causes was not obtained in the present study. Third, our research involved patients who were undergoing clinical CCTA, and whether our current findings can be applied to population-based samples is still unclear. Finally, we only considered diseases associated with inflammation and failed to consider other possible factors that may have an association with inflammation, such as the patient's diet. The primary findings of our study are summarized below: patients with high GlycA levels tended to show a higher incidence rate of MACE and all-cause death than those with low GlycA levels, and even after adjustments for critical covariables, a high GlycA level was considerably associated with elevated all-cause death and MACE among patients with no known CAD undergoing CCTA. To the best of our knowledge, this study is the first study to explore the relationship between the severity of CAD using CCTA in asymptomatic individuals, GlycA, and the risk of subsequent MACE and all-cause death.

Conclusion

Serum GlycA is significantly associated with the long-term clinical results of patients with no known CAD undergoing CCTA. Moreover, the risks of death and experiencing MACE increase in patients with high GlycA levels.

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