



# The prevalence of coronary atherosclerosis in patients with refractory gastroesophageal reflux disease ready for antireflux surgery

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### **Abstract**

Coronary atherosclerosis (CAS) and gastroesophageal reflux disease (GERD) share common risk factors. The existing CAS may not only increase the possibility of GERD to be refractory GERD (RGERD), but also increase the risk of antireflux surgery for these patients. The aim of this study was to estimate the prevalence of CAS and its potential risk factors in patients with RGERD ready for antireflux surgery. The retrospective analysis was performed in the digestive disease center of Suining Central Hospital, a teritary hospital in Sichuan, China. Records of patients with RGERD admitted to the hospital for antireflux surgery between July 2018, and June 2021 were included. The included patients were divided into the RGERD group and RGERD-CAS group based on the coronary computed tomography angiography (CCTA) results, which were defined as no CAS and CAS (<50% mild stenosis or ≥50% significant stenosis). In total, 448 patients with RGERD qualified for the study. The prevalence of CAS in these patients was 45.1%. Specifically, 246 patients (54.9%) were in the RGERD group, and 202 patients (45.1%) were in the RGERD-CAS group. Among these 202 patients with CAS, 120 patients (59.4%) had mild CAS (<50% stenosis), 82 patients (40.6%) had significant CAS (≥50% stenosis). Five independent risk factors, including male sex, high blood pressure (HBP), diabetes mellitus (DM), Barrett's esophagus (BE) and family history of coronary artery disease were identified for the occurrence of CAS in patients with RGERD ready for antireflux surgery after adjusting for other factors. CAS is prevalent in patients with RGERD ready for antireflux surgery. Routing CTTA was suggested to exclude potential coronary artery disease in RGERD patients ready for antireflux surgery with independent risk factors.

**Abbreviations:** AMI = acute myocardial infarction, BE = Barrett's esophagus, BMI = body mass index, CAD = coronary artery disease, CAS = coronary atherosclerosis, CCTA = coronary computed tomography angiography, DM = diabetes mellitus, GERD = gastroesophageal reflux disease, HBP = high blood pressure, PPIs = proton pump inhibitors, RE = reflux esophagitis, RGERD = refractory gastroesophageal reflux disease.

Keywords: antireflux surgery, coronary artery disease, coronary atherosclerosis, refractory gastroesophageal reflux disease

## 1. Introduction

Gastroesophageal reflux disease (GERD) is defined as a disorder in which gastric contents reflux recurrently into the esophagus, causing troublesome symptoms and/or complications.<sup>[1,2]</sup> The prevalence of GERD is high and increasing. The overall prevalence of GERD in adults is 13.3%, with a higher rate of 19.6% in Central America and 22.1% in South Asia.<sup>[3]</sup> GERD can result in diminished health-related quality of life, and potential long-term treatment can consume substantial health care resources.

"Refractory GERD" (RGERD) is defined as persisting objective GERD evidence despite medical therapy. Based on randomized trials, approximately 30% to 40% of GERD patients

receiving standard-dose proton pump inhibitors (PPIs) have an inadequate symptom response and/or inadequate endoscopic response at 8 weeks of treatment.<sup>[1]</sup> In practice, RGERD has been applied to the following 2 populations: an actual "GERD" population and a mixed population including GERD and conditions mimicking GERD.

Coronary artery disease (CAD) has been a common comorbid condition for GERD. GERD has also been considered a risk factor for acute myocardial infarction (AMI) CAD.<sup>[4,5]</sup> As the basis and precondition of CAD, the progression of coronary atherosclerosis (CAS) has been reported to be associated with reflux esophagitis (RE).<sup>[6]</sup> Recently, the increase in CAS has been reported to be 40.5% to 42.1% in the general population without myocardial infarction or coronary intervention,

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]

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and significant stenosis (≥50%) was reported to be 5.2% to 9.0%.<sup>[7,8]</sup> Simultaneously, the global prevalence of GERD has also been reported to be increased.<sup>[3,9]</sup> CAS and GERD share common risk factors and a common neurological pathway for their corresponding functions, which can make GERD and CAS interact and mutually reinforce each other.<sup>[10,11]</sup> On the one hand, gastroesophageal acid reflux via the vagal reflex may cause coronary hypoperfusion. On the other hand, products from the anaerobic metabolism of cardiomyocytes may cause the relaxation of the lower esophageal sphincter, facilitating reflux and making the reflux persistent and refractory. In addition, the corresponding medications for CAS and GERD may impair each other.<sup>[12]</sup>

Therefore, we hypothesize that a higher CAS can be found in patients with RGERD. Since antireflux surgery is one of the most standard treatment options for patients with RGERD, coexisting CAS, especially significant coronary artery stenosis, may increase the mortality and morbidity associated with the surgery. Thus, the purpose of this study was to estimate the prevalence of CAS in patients with RGERD who are preparing for antireflux surgery.

### 2. Materials and Methods

#### 2.1. Study design and patient selection

This is a retrospective review of patients with RGERD admitted to Suining Central Hospital for endoscopic or laparoscopic antireflux surgery from July 2018 to June 2021. The Suining Central Hospital institutional review board approved this study and waived informed consent for patients who provided research authorization. Data, analytic methods and study materials will be made available to other researchers upon request.

The inclusion criteria were as follows: patients qualified for the diagnosis of RGERD, and patients were admitted to the hospital to have antireflux endoscopic procedures or antireflux surgery. The exclusion criteria were as follows: patients who were not qualified for the diagnosis of RGERD; patients who had undergone upper gastrointestinal surgery before; and patients with malignant tumors, such as esophageal, gastric and/or pancreatic carcinoma. The health records were extensively reviewed for all of the qualified study participants. Records of baseline data, including sex, age, body mass index (BMI), which was calculated as weight (kg)/height<sup>2</sup> (m<sup>2</sup>), smoking and drinking status, and family history of early CAD, were collected. Routine blood and urine examinations and blood biochemical analyses, including cholesterol and triglycerides, were reviewed and analyzed. Records of endoscopy and coronary computed tomography angiography (CCTA) were reviewed. Patients were divided into the RGERD group and RGERD-CAS group based on the CTTA results, which were defined as no CAS and CAS (<50% mild stenosis or ≥ 50% significant stenosis).[7,13]

# 2.2. Definitions and diagnosis

The definition of RGERD is partially responsive or nonresponsive to a stable dose of a PPI during a treatment period of at least 8 weeks in patients with prior objective evidence of GERD. [1,14] Smoking status was recorded in medical records as current smokers and nonsmokers. Alcohol intake was medically recorded as drinking alcohol or not. The definition of dyslipidemia was according to the diagnostic criteria. Lipid abnormalities were classified according to the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults final report (NCEP-ATP III). [15] These classifications were the same as the criteria of the 2016 Chinese guidelines for the management of dyslipidemia in adults and

included the following: high TC level: ≥6.22 mmol/L; high LDL-C: ≥4.14 mmol/L; low HDL-C: < 1.04 mmol/L; and high TG: ≥ 2.26 mmol/L; non-HDL-C was calculated as TC minus HDL-C, and high non-HDL-C was defined as ≥4.9 mmol/L. [16,17] Dyslipidemia was diagnosed when the lipid value met any of these 5 criteria. The endoscopic diagnosis and classification of RE were performed according to the Los Angeles classification. [18] The diagnosis and classification of Barrett's esophagus (BE) were based on the Japan Esophageal Society classification of BE. [19] Sliding hiatal hernia (HH) is diagnosed when the apparent separation between the squamocolumnar junction and the diaphragmatic impression is greater than 2 cm as measured using the hash marks on the endoscope (spaced 5 cm apart) relative to the incisors. [20]

# 2.3. Statistical analysis

Statistical analysis was performed using SPSS 25.0 software (Statistical Product and Service Solutions, Chicago, IL). Categorical data are presented as percentages, while continuous data are presented as the means with standard deviations. The chi-square tests and independent sample *t* tests were used to analyze categorical and continuous variables. Logistic regression methods were applied for variables for the multivariate analysis. The odds ratios (ORs) and 95% confidence intervals (CI) were obtained. A 2-tailed *P* value <.05 was considered to be statistically significant.

#### 2.4. Ethical statement

This study was approved by the Institutional Review Board of the Suining Central Hospital in Suining and conducted in compliance with the ethical principles for medical research involving human subjects stated in the World Medical Association Declaration of Helsinki (version 2013). Informed consent was obtained from all subjects.

### 3. Results

# 3.1. Demographics and characteristics of the study subjects

From July 2018 to June 2021, 462 patients diagnosed with RGERD were admitted to Suining Central Hospital for antireflux endoscopic procedures or antireflux surgery. Except for the records of related medical history and CTTA were not complete enough for analysis in 14 patients, a total of 448 patients whose data were qualified for analysis (Fig. 1). The characteristics of the patients are shown in Table 1. There were 240 males (53.6%), 208 females (46.4%), and 48.5±11.2 years of age. The BMI was 23.8±3.6 kg/m². The risk factors, including a family history of early CAD, smoking status, drinking status, high blood pressure (HBP), diabetes mellitus (DM) and dyslipidemia, of the study patients are shown in Table 1. The reflux-related endoscopic findings, including RE, BE, and HH, are also listed in Table 1.

# 3.2. Prevalence of CAS in patients with RGERD

Based on the CTTA results, 246 patients (54.9%) were without CAS (RGERD group). Two hundred and two patients (45.1%) had different degrees of CAS (RGERD-CAS group) (Table 2). Thus, the prevalence of CAS in patients ready for antireflux surgery was 45.1%. Among these 202 patients with CAS, 120 patients (59.4%) had mild CAS (<50% stenosis), 82 patients (40.6%) had significant CAS ( $\ge$  50% stenosis) and 4 patients (2.0%) had significant stenosis and percutaneous coronary intervention (Fig. 1).

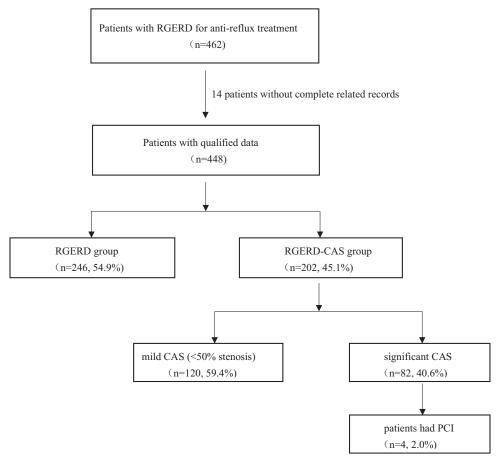


Figure 1. Flowchart of patients enrolled in this study. CAS = coronary atherosclerosis, PCI = percutaneous coronary intervention, RGERD = refractory gastro-esophageal reflux disease.

# Table 1 Demographics and characteristics of the study patients.

Parameters	Values
Number	448
Age, yr	$48.1 \pm 11.2$
Male, n (%)	240 (53.6)
BMI, kg/m <sup>2</sup>	$23.8 \pm 3.6$
Smoking, n (%)	111 (24.8)
Drinking, n (%)	73 (16.3)
HBP, n (%)	50 (11.2)
DM, n (%)	37 (8.3)
Family history of early CAD, n (%)	22 (4.9)
Dyslipidemia, n (%)	183 (40.8)
—TC, mmol/L	$5.2 \pm 1.0$
—LDL-c, mmol/L	$2.5 \pm 0.7$
—HDL-c, mmol/L	$1.5 \pm 0.5$
—TG, mmol/L	$1.7 \pm 1.0$
RE, n (%)	136 (30.4)
—LA grade A, n (%)	115 (84.6)
—LA grade B, n (%)	18 (13.2)
—LA grade C, n (%)	3 (2.2)
BE, n (%)	64 (14.3)
HH, n (%)	85 (19.0)

Results expressed as  $\bar{x}\pm SD$ .

 $BE = Barrett's \ esophagus, \ BMI = body \ mass \ index, \ CAD = coronary \ artery \ disease, \ DM = diabetes \ mellitus, \ HBP = high \ blood \ pressure, \ HDL-c = high-density \ lipoprotein \ cholesterol, \ HH = hiatal \ hernia, \ LDL-c = low-density \ lipoprotein \ cholesterol, \ RE = reflux \ esophagitis, \ TC = total \ cholesterol, \ TG = triglyiceride, \ LA = Los \ Angeles \ classification.$ 

# 3.3. Comparison of demographic and other general factors between the RGERD group and RGERD-CAS group

There were no differences between the 2 groups regarding mean age, alcohol drinking status, or BMI. However, more males (62.4% vs 46.3%, P=.005) and more smokers (30.7% vs 19.9%, P=.020) were found in the RGERD-CAS group than in the RGERD group. Compared to the RGERD group, the proportions of patients with HBP (16.8% vs 6.5%, P<.001), DM (13.4% vs 4.1%, P<.001), family history of early CAD (9.4% vs 1.4%, P<.001) and dyslipidemia (48.5% vs 34.6%, P=.001) were statistically higher in the RGERD-CAS group (Table 2).

Regarding the reflux-related endoscopic findings, the proportion of patients diagnosed with RE was slightly higher in the RGERD-CAS group than in the RGERD group (31.7% vs 29.3%). However, no statistically significant difference was found between them (P = .658). However, a statistically significant difference was found regarding BE findings between the 2 groups. In the RGERD-CAS group, more patients with BE were found compared to the RGERD group (18.8% vs 10.6%, P = .023). Regarding HH, which is one of the important mechanisms for refractory reflux, no statistically significant difference was found for the presence of HH between the 2 groups (18.4% vs 20.0%, P = .596) (Table 2).

# 3.4. Comparison of factors among RGERD and RGERD-CAS groups using binary logistic regression analysis

Binary logistic regression analysis was performed for the following parameters between the RGERD group and RGERD-CAS group: male sex, smoking, HBP, DM, dyslipidemia, RE and family history of early CAD. Statistically significant differences were identified in the univariate analysis (Table 2).

Table 2
Comparison of demographics and characteristics of RGERD group and RGERD-CAS group.

Parameters	RGERD	RGERD-CAS	P value	
Number, n (%)	246 (54.9)	202 (45.1)	_	
Age, yr	47.9 ± 11.6	$48.2 \pm 12.5$	.654	
Male, n (%)*	114 (46.3)	126 (62.4)	.005	
BMI, kg/m <sup>2</sup>	$23.5 \pm 3.5$	$24.0 \pm 3.9$	.336	
Smoking*	49 (19.9)	62 (30.7)	.020	
Drinking	51 (14.7)	22 (21.8)	.096	
HBP*	16 (6.5)	34 (16.8)	.000	
DM*	10 (4.1)	27 (13.4)	.000	
Family history of early CAD*	3 (1.4)	19 (9.4)	.000	
Dyslipidemia*	85 (34.6)	98 (48.5)	.001	
—TC*	$5.0 \pm 1.0$	$5.7 \pm 1.1$	.003	
—LDL-c*	$2.3 \pm 0.7$	$2.7 \pm 0.5$	.010	
—HDL-c	$1.6 \pm 0.4$	$1.5 \pm 0.6$	.592	
—TG	$1.6 \pm 0.8$	$1.7 \pm 0.7$	.763	
RE	72 (29.3)	64 (31.7)	.658	
LA grade A	62 (86.1)	53 (82.8)	.744	
LA grade B	9 (12.5)	9 (14.1)	.258	
LA grade C	1 (1.4)	2 (3.1)	.187	
LA grade D	0	0	-	
BE*	26 (10.6)	38 (18.8)	.023	
HH	45 (18.4)	40 (20.0)	.596	

BE = Barrett's esophagus, BMI = body mass index, CAD = coronary artery disease, CAS = coronary atherosclerosis, DM = diabetes mellitus, HBP = high blood pressure, HDL-c = high-density lipoprotein cholesterol, HH = hiatal hernia, LA = Los Angeles classification, LDL-c = low-density lipoprotein cholesterol, RE = reflux esophagitis, RGERD = refractory gastroesophageal reflux disease, TC = total cholesterol, TG = triglyiceride.

The assignments of factors related to CAS in patients with RGERD are shown in Table 3. Five independent risk factors for the occurrence of CAS in patients with RGERD were identified after adjusting for other factors. Male sex (OR = 1.918, 95% CI: 1.142-3.220, P=.014), HBP (OR = 5.200, 95% CI: 2.315-11.679, P<.001), DM (OR = 8.085, 95% CI: 1.766-37.012, P=.007), BE (OR = 2.208, 95% CI: 1.109-4.396, P=.024) and family history of CAD (OR = 7.844, 95% CI: 1.851-33.251, P=.005) were positive predictive factors for the occurrence of CAS in patients with RGERD (Table 4).

# 4. Discussion

This study retrospectively investigated the comorbidity of CAS in patients with RGERD that were preparing for antireflux surgery. The primary findings of this study are that CAS was very common in patients with RGERD ready for antireflux surgery, with 45.1% of study patients having CAS. In addition, 2.0% of patients with significant stenosis had a percutaneous coronary

Table 3

Assignment table of variables in patients with RGERD and patients with RGERD-CAS.

Factors	Variables	<b>Explanation of assignments</b>
Gender	X1	Female = 0, Male = 1
Smoking	X2	Without smoking $= 0$ , Smoking $= 1$
HBP	Х3	Without $HBP = 0$ , $HBP = 1$
DM	X4	Without $DM = 0$ , $DM = 1$
BE	X5	Without $BE = 0$ , $RE = 1$
Dyslipidemia	X6	Without dyslipidemia = 0, dyslipidemia = 1
Family history of early CAD	X7	Without CAD history $= 0$ , with $= 1$
CAS	Υ	RGERD with $CAS = 1$

CAD = coronary artery disease, CAS = coronary atherosclerosis, DM = diabetes mellitus, HBP = high blood pressure, RGERD = refractory gastroesophageal reflux disease.

intervention. Five independent risk factors, including male sex, HBP, DM, family history of CAD and BE, were positively correlated with the occurrence of CAS in patients with RGERD ready for antireflux surgery.

Previous data on the prevalence of CAS in patients with RGERD are rare. A number of studies have reported the prevalence of CAS in the general population.<sup>[7,8]</sup> Bergström et al<sup>[7]</sup> performed a study in a middle-aged population without previous myocardial infarction or coronary intervention, which reported that 42.1% of participants had atherosclerotic plaques in their coronary arteries and significant stenosis (≥50%) was reported in 5.2% of the study population. In an Asian study that included 6311 patients without a prior history of CAD, after age and gender adjustment, the prevalence of CAS plaque was 40.5%, and significant CAS was observed in 9.0%.[8] However, a higher prevalence of the CAS rate (45.1%) was found in patients with RGERD in our study. Two reasons may contribute to this difference. First, our study subjects were patients with RGERD preparing for antireflux surgery. A previous study reported that GERD patients had a greater probability of CAD than those without GERD, and arteriosclerosis parameters were also reported to be higher in patients with HH whose antireflux barrier had major defects than those without HH.[21,22] The potential correlation might be from the common neurological control mechanisms for the esophagus and coronary arteries. Since gastroesophageal acid reflux via the vagal reflex may cause coronary hypoperfusion, the products of anaerobic metabolism of cardiomyocytes may cause relaxation of the lower esophagus sphincter, facilitating reflux, which may lead to a higher occurrence of CAD and a refractory reflux condition. [23] Second, the relative long-time prescription of PPIs in patients with RGERD. It has been reported that PPIs can reduce cardiac contractility and raise the risk of atherosclerosis by increasing the serum levels of homocysteine.[12]

However, one may ask why we chose patients with RGERD ready for antireflux surgery as our study subjects. Two reasons may contribute to this. First, GERD has long been reported to be an independent risk factor for CAD, especially for AMI, which is the most important and fatal complication of CAS. Eisa et al<sup>[5]</sup> included 200,400 patients with GERD and 386,800 without GERD to compare the incidence of AMI in patients with and without GERD. The odds of developing AMI in the GERD population were 1.11, and GERD patients had higher odds of developing AMI than males with obesity. This high risk of developing AMI in GERD patients was also confirmed by another large population-based study that included a total of 54,442 newly diagnosed GERD patients and 269,572 randomly selected controls. During a mean follow-up period of 3.3 years. Based on Cox proportional hazard model analysis, GERD was independently associated with an increased risk of developing AMI, with a hazard ratio of 1.48.[21] Second, CAS is the basis for perioperative cardiovascular complications, especially fatal AMI. Cardiovascular complications are the major contributors to morbidity and mortality after noncardiac surgery. The perioperative AMI was reported to be 0.9% to 16.0% in patients undergoing noncardiac surgery.[24,25] Despite early detection during routine clinical screening, it is associated with substantial short- and long-term mortality. [24] As a single center, we also learned lessons from a male aged 61 who complicated AMI 30 hours after endoscopic esophageal radiofrequency treatment for RGERD. Although he survived and recovered smoothly after timely percutaneous transluminal coronary intervention, we retrospectively analyzed his medical history. We found that he had many risk factors, including male sex, smoking and HBP, for the occurrence of AMI. Unlike spontaneous myocardial infarction, perioperative myocardial infarction occurred during the perioperative period when he tended to be under a state of stress, together with anesthetic interference, intraoperative blood loss, and postoperative pain. In addition, the delivery of esophageal radiofrequency adjacent to the coronary artery may

<sup>\*</sup>Differences were considered significant when P < .05.

Table 4
Factors associated with the occurrence of CAS in patients with RGERD by binary logistic regression analysis.

Factors	RGERD	RGERD-CAS	OR (95% CI)	P value
Male	114 (46.3)	126 (62.4)	1.918 (1.142–3.220)	.014*
Smoking	49 (19.9)	62 (30.7)	0.972 (0.516–1.833)	.931
HBP	16 (6.5)	34 (16.8)	5.200 (2.315–11.679)	.000*
DM	10 (4.1)	27 (13.4)	8.085 (1.766–37.012)	.007*
Dyslipidemia	85 (34.6)	98 (48.5)	1.060 (0.609-1.845)	.838
BÉ	66 (10.6)	38 (18.8)	2.208 (1.109-4.396)	.024*
Family history of CAD	3 (1.4)	19(9.4)	7.844 (1.851–33.251)	.005*

BE = Barrett's esophagus, CAD = coronary artery disease, CAS = coronary atherosclerosis, CI = confidence intervals, DM = diabetes mellitus, HBP = high blood pressure, OR = odds ratio, RGERD = refractory gastroesophageal reflux disease.

be another important incentive factor for atherosclerotic plaque detachment from the coronary artery.

Another important finding of our study was that 5 independent risk factors, including male sex, HBP, DM, family history of CAD and BE, were positively related to the occurrence of CAS in patients with RGERD. The first 4 risk factors have long been reported and proven to be risk factors for CAS. [26,27] Regarding BE with CAS in patients with RGERD, few studies have reported BE alone until now. Our previous study reported that GERD is very common in patients with CAD and refractory chest pain, and 49% of chest pain is associated with acid reflux due to GERD. In patients with GERD, a higher incidence and longer duration of ischemic events were observed.<sup>[4]</sup> Theoretically, it is possible that BE, as a complication of GERD, might be expected in patients with CAD. A previous study reported that the inflammatory markers IL-6, IL-8, and NF-kappaB were significantly associated with the severity of CAS and associated with BE.[28-30] However, further study is still required to investigate whether this is the potential mechanism to correlate BE with CAS.

However, there are also several potential limitations of this study. First, we did not include all subjects with RGERD. The strict inclusion criteria possibly resulted in some bias. As a retrospective study, it could be difficult to find a CTTA result for every patient in outpatient clinics since CTTA is not a routine test for general patients with RGERD. In fact, only a few patients with RGERD are necessary to have a CTTA to exclude potential CAS. However, CTTA could be a routine test to exclude significant CAS before surgery in patients with RGERD ready for antireflux surgery. Besides, carotid ultrasound can be a choice to screen patients with CAS in consideration of the potential X ray radiation hazard and relative high cost of CCTA. It has been reported that the presence of plaque diagnosed by carotid ultrasound correlated with CCTA findings with a high specificity (92.8%).[31] In addition, the patients preparing for surgery can be the right and appropriate representation of patients with RGERD who are not responsive to traditional medical treatment. We plan to perform a prospective study to investigate the prevalence of CAS in general patients with RGERD in our next study. Second, the sample size is relatively small. However, all of the patients presented here were well defined and homogeneous. Third, the possible association between the severity of GERD and the severity of CAS was not assessed in our study. Since some patients received a 24-hour pH and/or a pH-metry/impedance test, some had only an endoscopic diagnosis of LA grade B or more severe than grade B. It could be difficult to standardize and correlate the severity of GERD with CAS. However, this could be compensated for in our next prospective study. Fourth, a detailed investigation was not performed to analyze and compare the characteristics of patients with different severities of CAS. Since one of our perioperative AMIs occurred in a patient with mild stenosis (<50%) after endoscopic esophageal radiofrequency therapy, we have reason to believe that no matter how severe the CAS is, once there is an atherosclerotic plaque, it has

the potential to detach from the coronary artery with an inducing factor, such as adjacent esophageal radiofrequency. We plan to investigate the correlation of the calcium score, atherosclerotic plaque characteristics and RGERD in our next study.

## 5. Conclusion

The results from our study indicate that CAS was very common in patients with RGERD preparing for antireflux surgery. Five independent risk factors, male sex, HBP, DM, BE and family history of CAD, were positive predictive factors for the occurrence of CAS in these patients. Routing CTTA was suggested to be performed in RGERD patients preparing for antireflux surgery with these risk factors.

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## **Author contributions**

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