Original Article

Prognosis value of EAS index in patients with obstructive coronary artery disease

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Background: EAS index is reported to be an adjunctive tool for risk stratification in addition to left ventricular ejection fraction (LVEF). This study aimed to verify the predictive value of EAS index among coronary artery disease (CAD) patients with different cardiac systolic function levels.

Methods: A total of 477 patients with obstructive CAD were included in the exploratory analysis of a prospective cohort between October 2017 and January 2018 at Guangdong Provincial People's Hospital. EAS index, e'/(a' × s'), is a novel parameter assessed by tissue Doppler imaging (TDI) indicating combined diastolic and systolic performance. Any occurrence of major adverse cardiovascular event (MACE) was recorded, including first onset of myocardial infarction, stroke, readmission for heart failure, coronary revascularization, or cardiovascular death that occurred within 6 months of the first admission. Kaplan-Meier survival and Cox regression analyses were applied to testify the predictive value of EAS index for cardiovascular outcome.

Results: A total of 415 patients (87.2%) completed the follow-up (median, 25.9 months) and experienced 101 (24.3%) MACEs, 17 (4.0%) deaths, and 139 (33.4%) composite events. Elevated EAS index was significantly associated with a higher incidence of MACE, even after adjustment for age, sex, body mass index, N-terminal pro brain natriuretic peptide, high-sensitivity troponin T, high-density lipoprotein, stenosis degree, and other TDI parameters [Model 3, hazard ratio: 1.81, 95% confidence interval (CI): 1.15–2.85]. For different levels of cardiac function, Kaplan-Meier survival analysis revealed that elevated EAS index was associated with higher MACE incidence only in patients with LVEF ≥50% ($P<0.05$).

Conclusions: EAS index is an independent predictor of MACE in patients with obstructive CAD, which could be utilized as a tool for risk stratification in CAD patients or incorporated into a prediction model to improve efficacy.

Keywords: EAS index; coronary artery disease (CAD); major adverse cardiovascular event (MACE); tissue Doppler imaging (TDI); prognosis

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Introduction

Coronary artery disease (CAD) has always been one of the primary diseases affecting human health worldwide and remains the leading global cause of mortality (1). CAD can cause a range of cardiac dysfunction, including left ventricular diastolic and systolic function declines (2). A previous study showed that left ventricular dysfunction is associated with poor prognosis in CAD patients (3). Therefore, accurate evaluation of the indicators related to left ventricular function can more comprehensively evaluate the prognosis of patients with CAD.

As a common diagnostic method, tissue Doppler imaging (TDI) is non-invasive, simple, inexpensive, and can accurately evaluate left ventricular function (2). TDI-derived parameters have high prognostic value for cardiovascular diseases, such as CAD and heart failure (HF) (4). Indexes such as mitral annular systolic (s'), early diastolic (e'), and late diastolic (a') velocities, and the transmitral to mitral annular early diastolic velocity ratio (E/e') have all been shown to predict mortality or cardiovascular events among the general population, patients with HF, and CAD patients with relatively high disease severity levels (5-7). Recently, EAS index, as a novel indicator for combined evaluation of diastolic and systolic function, was reported to be an adjunctive tool for risk stratification in addition to left ventricular ejection fraction (LVEF) in the general population and among HF patients (7-9). However, the predictive role of the TDI-derived EAS index in patients with obstructive CAD is unclear. It is assumed that EAS index might have the ability to capture subtle cardiac dysfunction before the systolic or diastolic function is significantly impaired.

Therefore, we attempted to examine the predictive value of EAS index in a prospective cohort of patients with obstructive CAD at different levels of cardiac systolic function. Through these comparisons, we intended to substantiate whether EAS index is an accurate predictor for cardiovascular outcomes in addition to LVEF. The aim of this study was to determine the predictive value of EAS index in CAD patients, particularly in those with preserved ejection fraction. We present this article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-109/rc).

Methods

Study population

The current study was a prospective cohort of patients with obstructive CAD and a post hoc exploratory analysis on the basis of follow-up outcomes (10,11). A total of 705 consecutive patients with primary admitting diagnoses of stable CAD were enrolled in the survey between October 2017 and January 2018 at Guangdong Provincial People's Hospital. There was no urgency for emergency revascularization therapy or intensive care. The present study included adult obstructive CAD patients who underwent an echocardiographic examination with color TDI. Patients with severe structural heart disease such as coronary artery fistula, cardiomyopathy, and severe valvular disease, were excluded.

All participants gave written informed consent before they were included in the study. The study was performed in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2017203H).

Coronary angiography

Coronary angiography was performed by a team of experienced cardiac interventionists at Guangdong Provincial People's Hospital. Obstructive CAD was defined as 1 or more of the 3 main vessels with stenosis ≥50% (12), and severity of coronary stenosis was defined as 1/2/3 branch lesions with the highest severity being ≥30% luminal stenosis in the left main coronary artery. The history of revascularization was defined as performing coronary stenting or coronary artery bypass grafting surgery during this hospitalization.

Echocardiography

Data on conventional transthoracic echocardiography (TTE) including TDI measurements were directly acquired from clinical records. A GE Vivid E9 imaging system (GE

Vingmed Ultrasound, Horten, Norway) equipped with a probe M5S (2, 4 MHz), or a Philips IE33 imaging algorithm (Philips Healthcare, Andover, MA, USA) with a S5-1 probe (2.5, 3.5 MHz) was employed. All echocardiographic data were collected according to the guidelines of the American Society of Echocardiography (ASE).

LVEF was measured based on the modified method of biplane Simpson's. TDI measurements including systolic velocity (s'), early (e'), and late (a') diastolic velocities were recorded at the septal mitral annulus in apical 4-chamber view (13). The transmitral to mitral annular early diastolic velocity ratio (E/e') was calculated (14,15). We also defined the ratio of early and late diastolic velocities as the e'/a' ratio (16). Ratios of E/e' and e'/a' represented measures of left ventricular filling pressure and diastolic performance, respectively. EAS index, a novel parameter calculated as e'/(a' × s'), is a combined assessment of cardiac systolic and diastolic function (7,17).

Outcomes

Follow-up data were obtained 6 months after first admission and then yearly through a scripted telephone interview. The follow-up for all patients took place at the same time each year. Respondents were asked to provide detailed information about their medical history including myocardial infarction (MI), stroke, coronary revascularization, cardiac or noncardiac rehospitalization, and death. A major adverse cardiovascular event (MACE) was defined as the first onset of MI, stroke, coronary revascularization, readmission for HF, or cardiovascular death. A composite endpoint referred to more than 1 event mentioned above.

Statistical analysis

Categorical variables were reported as frequency (percentages) and analyzed with chi-square or Fisher's exact tests. Continuous variables were represented as mean ± standard deviation and compared with Student's *t*-tests if they followed normal distributions, otherwise they were represented as median (inter quartile range) and compared with Wilcoxon rank-sum tests. The overall impact of the EAS index on MACE among the general population and patients with LVEF ≥50% were demonstrated using Kaplan-Meier survival curves and compared by the log-rank test. Cox regression models were applied to determine the main predictors for MACE including composite outcomes. All the possibly correlated factors (P<0.10) were gathered to compare patients with and without MACE using forward selection methods. Model 1 was a multivariate Cox regression model including demographic factors. Model 2 included demographic and clinical characteristics in multivariable logistic regression analysis. Model 3 was a multivariate logistic regression model including other TDI indicators and all control variables mentioned. Receiver operating characteristic (ROC) analysis was applied to evaluate the predictive value of EAS index for MACE and area under the ROC curve (AUC) was calculated. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA). All tests were 2-sided, and P values <0.05 were considered statistically significant.

Results

A total of 477 patients with obstructive CAD were finally included after excluding 35 patients without coronary angiography, 97 patients with coronary artery stenosis <50%, 12 patients with coronary fistula, cardiomyopathy, severe valvular disease, or aortic stenosis. Cases without complete TTE or TDI data were further excluded from the analysis, leaving 477 patients in the final sample (*Figure 1*).

A total of 415 patients (87.0%) completed the follow-up (median, 25.9 months) and experienced 101 (24.3%) MACEs including 16 (3.8%) nonfatal strokes, 44 (10.6%) noncardiac rehospitalizations, 17 (4.0%) deaths, and 139 (33.4%) composite events.

Population characteristics

The baseline clinical characteristics of enrolled cases were summed up and are displayed in *Table 1* and Table S1. The group with MACE had significantly higher N-terminal pro brain natriuretic peptide (NT-proBNP), high-sensitivity troponin T (Hs-TNT), degree of coronary stenosis, left ventricular end-systolic diameter, E/e', e'/a', and EAS index than the group without MACE (*Table 1*). However, LVEF and a' were significantly lower in the MACE group (P=0.001 and P<0.001 respectively), whereas there was no significant difference in other characteristics between the 2 groups (all P>0.05).

The group with elevated EAS index had higher NT-proBNP, Hs-TNT, rate of furosemide use, e', E/e', and e'/a' but lower rate of calcium channel blocker use, body mass index (BMI), LVEF, and a' than the group with lower EAS index in all patients (Table S1). In addition, patients with

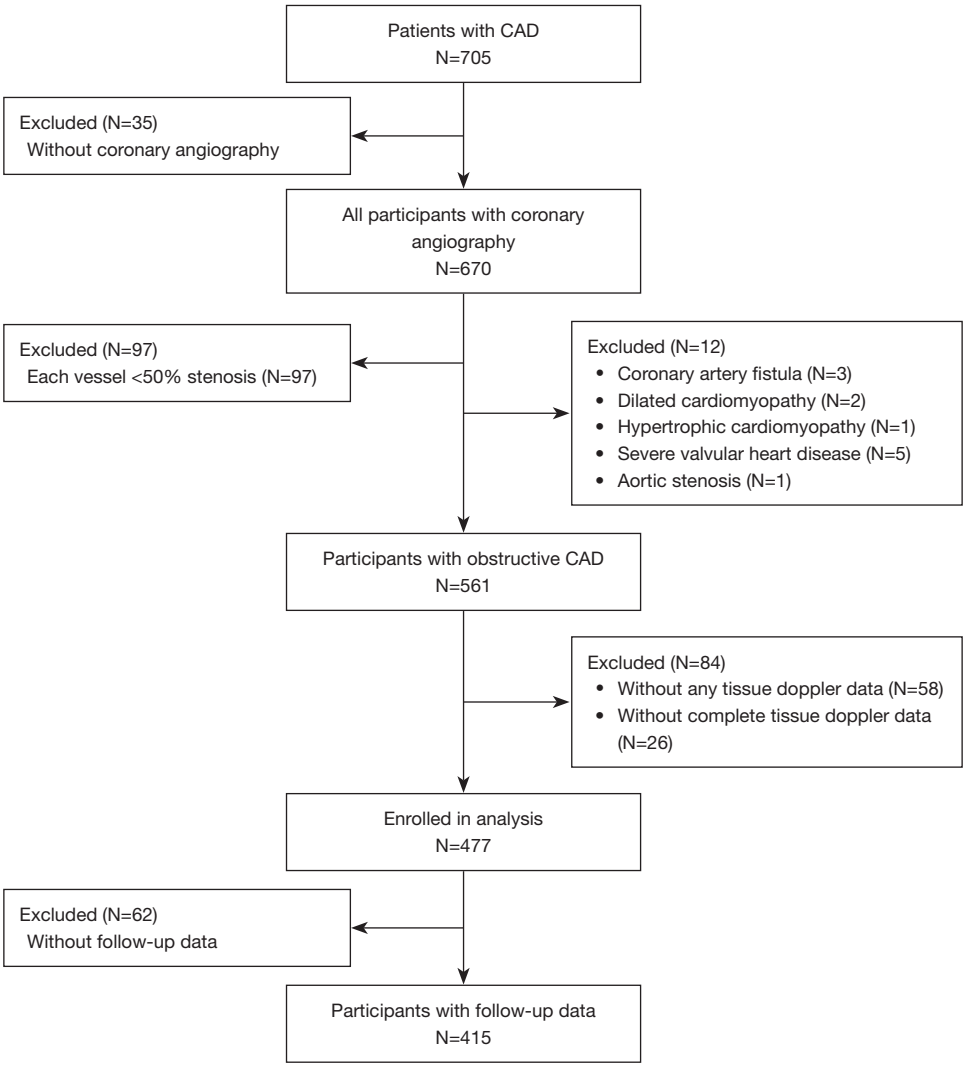

Figure 1 Screening flow of patients included in the research. Obstructive CAD was defined as 1 or more of the 3 main vessels with stenosis ≥50%, confirmed by coronary angiography or with a history of coronary artery bypass grafting or coronary stent implantation. CAD, coronary artery disease.

higher EAS index were more likely to have experienced MACEs and composite events. However, there was no significant difference in LVEF between the 2 groups among patients with LVEF ≥50% (P=0.15).

EAS index as the main predictor for MACE and composite events

According to *Table 2*, only elevated EAS index was significantly associated with a higher incidence of MACE [unadjusted, hazard ratio (HR): 1.76, 95% confidence interval (CI): 1.18–2.63, P=0.006], even after adjustment for multivariable confounding factors including age, sex, BMI, NT-proBNP, Hs-TNT, high-density lipoprotein cholesterol (HDL-C), stenosis degree, and conventional TDI parameters e', a', s', E/e', and e'/a' (Model 3, HR: 1.81, 95% CI: 1.15–2.85, P=0.01).

Figure 2 shows the association between EAS index and MACE in the general population and patients with different levels of LVEF. Kaplan-Meier survival analyses further demonstrated that elevated EAS index was significantly associated with MACE in the general population (HR: 1.88, 95% CI: 1.25–2.82, P=0.005). For the different levels of cardiac function, elevated EAS index

Table 1 Baseline clinical characteristics according to cardiovascular outcomes among the study population

Variables	Overall, n=477	Patients with follow-up data (n=415)		
		Without MACE, n=314	With MACE, n=101	P value
Age, years	64±10	63±9	63±11	0.93
Male sex	364 (76.3)	238 (75.8)	71 (70.3)	0.27
Body mass index, kg/m^2	24.2 (22.4, 26.2)	24.1 (22.4, 26.4)	24.5 (22.3, 26.2)	0.78
NT-proBNP, pg/mL	190.3 (62.3, 714.2)	157.5 (59.6, 487.2)	318.4 (56.0, 1619.8)	0.01
Hs-TNT, pg/mL	15.3 (9.1, 58.8)	12.8 (8.4, 37.5)	21.9 (11.5, 111.3)	0.001
CCR, mL/min	92.3 (81.5, 106.2)	91.1 (81.2, 103.9)	92.2 (79.4, 109.3)	0.32
LDL-C, mmol/L	2.7 (2.2, 3.4)	2.7 (2.3, 3.4)	2.8 (2.2, 3.3)	0.74
HDL-C, mmol/L	0.9 (0.8, 1.1)	1.0 (0.8, 1.1)	0.9 (0.8, 1.0)	0.01
Hypertension	299 (62.7)	199 (63.4)	62 (61.4)	0.72
Diabetes	168 (35.2)	108 (34.4)	36 (35.6)	0.82
History of revascularization	161 (33.8)	97 (30.9)	40 (39.6)	0.11
Stenosis degree				0.03
1	89 (18.7)	69 (22.0)	10 (9.9)	
2	98 (20.5)	61 (19.4)	21 (20.8)	
3	290 (60.8)	184 (58.6)	70 (69.3)	
History of medicine				
ACEI/ARB	356 (74.6)	231 (73.6)	80 (79.2)	0.26
Mono or dual antiplatelet	471 (98.7)	310 (98.7)	99 (98.0)	0.64
Statin	466 (97.7)	311 (99.0)	97 (96.0)	0.06
β-blocker	415 (87.0)	271 (86.3)	92 (91.1)	0.21
CCB	117 (24.5)	76 (24.2)	27 (26.7)	0.61
Furosemide	57 (11.9)	29 (9.2)	16 (15.8)	0.06
LVEDD, mm	47.0 (44.0, 51.0)	47.0 (44.0, 50.0)	47.0 (44.0, 53.0)	0.15
LVESD, mm	30.0 (27.0, 36.0)	30.0 (26.0, 34.0)	31.0 (27.0, 40.0)	0.006
LVEF, %	62.0 (53.0, 65.0)	62.0 (57.0, 65.0)	60.0 (44.5, 64.0)	0.001
Peak early diastolic velocity (e'), cm/s	5.0 (4.3, 6.2)	5.1 (4.3, 6.4)	5.0 (4.4, 6.3)	0.79
Peak late diastolic velocity (a'), cm/s	9.0 (7.0, 10.0)	9.0 (7.9, 10.0)	8.0 (6.0, 10.0)	<0.001
Peak systolic velocity (s'), cm/s	7.0 (6.0, 8.0)	7.0 (6.0, 8.0)	6.5 (5.0, 8.0)	0.08
E/e'	12.0 (10.0, 15.0)	12.0 (10.0, 14.0)	13.0 (10.0, 16.8)	0.02
e'/a'	0.6 (0.5, 0.8)	0.6 (0.5, 0.8)	0.7 (0.6, 0.8)	0.007
EAS index, s/m	9.15 (7.26, 12.5)	8.9 (7.1, 11.6)	10.4 (8.1, 15.9)	0.001

Data are presented as mean ± standard deviation, median (interquartile range), or number (%). MACE, major adverse cardiovascular event; SD, standard deviation; IQR, interquartile range; NT-proBNP, N-terminal pro brain natriuretic peptide; Hs-TNT, high sensitivity troponin T; CCR, creatinine clearance rate; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction.

Table 2 TDI predictors of MACE by cox regression models[†]

Variables	Unadjusted		Model 1		Model 2		Model 3	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
e' ≥5.0 *vs.* <5.0	0.89 (0.58–1.35)	0.57	0.90 (0.58–1.39)	0.63	1.08 (0.63–1.86)	0.78	0.72 (0.37–1.38)	0.63
a' <9.0 *vs.* ≥9.0	1.78 (1.19–2.65)	0.005	1.78 (1.19–2.65)	0.005	1.83 (1.17–2.88)	0.008	1.10 (0.61–1.98)	0.08
s' <7.0 *vs.* ≥7.0	1.50 (1.02–2.22)	0.04	1.50 (1.02–2.22)	0.04	1.26 (0.79–2.02)	0.33	0.82 (0.44–1.54)	0.97
e'/a' ≥0.6 *vs.* <0.6	1.68 (1.09–2.57)	0.02	1.68 (1.09–2.57)	0.02	1.92 (1.17–3.15)	0.01	1.76 (0.90–3.44)	0.07
E/e' ≥12.0 *vs.* <12.0	1.43 (0.94–2.16)	0.09	1.42 (0.93–2.18)	0.11	1.16 (0.71–1.92)	0.55	1.25 (0.74–2.14)	0.21
EAS ≥9.15 *vs.* <9.15	1.76 (1.18–2.63)	0.006	1.76 (1.18–2.63)	0.006	1.84 (1.18–2.89)	0.008	1.81 (1.15–2.85)	0.01

[†], Model 1: adjusted for age, sex; Model 2: adjusted for age, sex, BMI, NT-proBNP, Hs-TNT, HDL-C, stenosis degree; Model 3: adjusted for age, sex, BMI, Nt-proBNP, hs-TNT, HDL-C, stenosis degree, e', a', s', E/e', e'/a', EAS index. Note: e', a', s', E/e', e'/a', EAS index, sex and stenosis degree were included in the model as categorical variables. TDI, tissue Doppler imaging; MACE, major adverse cardiovascular event; BMI, body mass index; NT-proBNP, N-terminal pro brain natriuretic peptide; Hs-TNT, high sensitivity troponin T; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; CI, confidence interval.

was significantly associated with higher MACE incidence only in patients with LVEF ≥50% (HR: 1.74, 95% CI: 1.06–2.84, P=0.02).

In addition, Cox regression analyses found that a', s', E/e', and EAS index were all correlated with composite events in the unadjusted model (Table S2). However, after adjusting for other factors, only a' was statistically associated with the incidence of composite events (adjusted HR:1.85, 95% CI: 1.27–2.30, P=0.001).

ROC analyses for EAS index in predicting MACE

ROC analyses demonstrated that elevated EAS index had passable predictive value for MACE in both patients with LVEF ≥50% (AUC =0.56, P=0.12) and the general population (AUC =0.58, P=0.032) (*Table 3*). With the addition of HDL-C, BNP, and LVEF, AUC could be further increased among patients with preserved LVEF (AUC =0.61, P=0.042) and the general population (AUC =0.64, P<0.001).

Discussion

In this prospective cohort study, we demonstrated that EAS index was an independent predictor for MACE for patients with obstructive CAD. In addition, in subgroup analysis, we found that EAS index was significantly associated with MACE in patients with preserved LVEF, rather than those with reduced LVEF.

EAS index and prognosis

According to prior studies (8,18,19), e' (mitral annulus early diastolic velocity) reflects left ventricular relaxation, and s' (systolic annular velocity) reflects left ventricular systolic function. Both e' and s' decrease early in the deterioration process of cardiac function. In contrast, a' (late diastolic annular velocity) reflects passive ventricular motion and is dependent on the left ventricular stiffness and left atrial contractility. Given that the influence of increased left ventricular stiffness is most pronounced in late diastole (20), a' received more impact than e'. This results in the augment in e'/a', reflecting the progress in deterioration of cardiac function. Since early diastolic performance is partly conditioned by systolic performance, low s' usually induces low e'. However, high preload in patients with severe cardiac dysfunction may partially blunt such a damaging effect (8). To summarize, a high EAS index indicates increased preload with systolic dysfunction, diastolic dysfunction, or both (9).

EAS index has been reported to be a highly effective means of differentiation between patients with different cardiac function levels (21). In our research, striking discrepancies in e', a', and s' were found between groups categorized by EAS index in patients with LVEF >50%, while LVEF and E/e' showed no difference during the comparisons.

EAS index, compared to other TDI parameters such as the E/e' ratio, has been proven to be an accurate estimator of both cardiac systolic and diastolic function, as well as an excellent predictor of cardiovascular prognosis in the general population (7) and HF patients (8,21). Our study

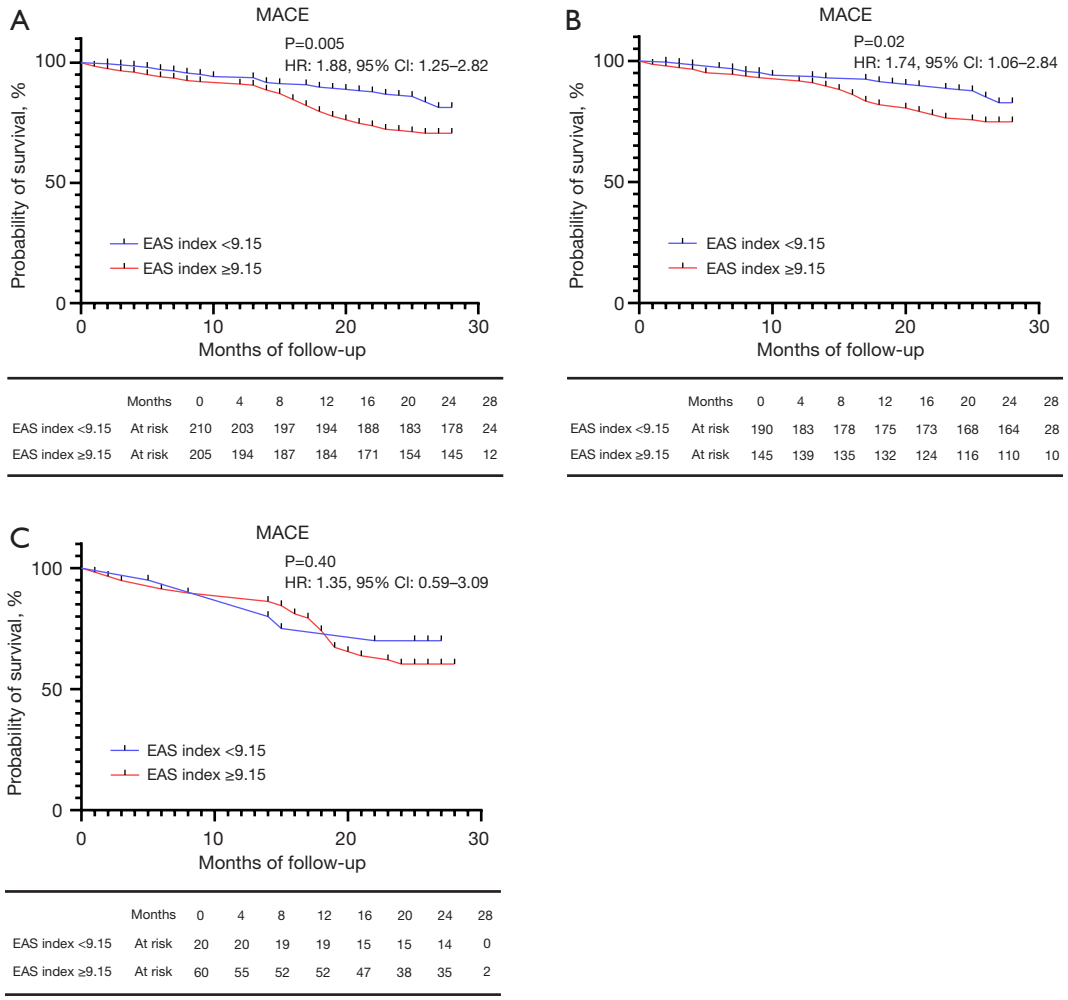

Figure 2 Kaplan-Meier survival analyses of elevated EAS index (≥9.15) for MACE events among patients with different cardiac systolic function levels. (A) The association between the EAS index and MACE events in all patients; (B) the association between the EAS index and MACE events in patients with LVEF ≥50%; (C) the association between the EAS index and MACE events in patients with LVEF <50%. Elevated EAS index was only associated with worse cardiovascular prognosis in all patients and patients with preserved LVEF, but not in patients with LVEF <50%. MACE, major adverse cardiovascular event; LVEF, left ventricular ejection fraction; HR, hazard ratio, CI, confidence interval; SE, standard error of the mean.

confirmed and extended these findings in obstructive CAD patients. According to our results, EAS index could well predict cardiovascular prognosis, even in patients with preserved LVEF, which showed that the predictive value seemed to be only associated with cardiac function.

Echocardiography has been validated as a noninvasive and repeatable examination method for prognosis estimation (22). The unique feature of EAS index to predict cardiovascular outcomes in patients with preserved LVEF may lie in its ability to concurrently reflect systolic and diastolic performance. Besides, elevated EAS index is reported to be associated with mental stress-induced myocardial ischemia (23), which has been linked to poor cardiovascular prognosis in CAD patients (24). Further research is needed to explore the mechanisms that underlie the prognostic effect of EAS index.

Implications and significance

Our findings indicated that EAS index is superior to

Table 3 Predictive value of EAS index for MACE by ROC analysis in CAD patients with LVEF ≥50% and the whole population

Groups	ROC association statistics			
	AUC	Standard error	95% CI	P value
LVEF ≥50%				
Elevated EAS index	0.56	0.039	0.49–0.64	0.12
HDL-C	0.59	0.038	0.51–0.66	0.027
BNP	0.52	0.046	0.43–0.61	0.52
EAS index + HDL-C+ BNP	0.61	0.042	0.53–0.69	0.042
All patients				
Elevated EAS index	0.58	0.032	0.52–0.64	0.032
HDL-C	0.58	0.031	0.52–0.64	0.031
LVEF	0.61	0.034	0.54–0.67	0.001
EAS index + HDL-C+ LVEF	0.64	0.032	0.58–0.70	<0.001

MACE, major adverse cardiovascular event; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; ROC, receiver operating characteristic; AUC, area under the curve; CI, confidential interval; HDL-C, high-density lipoprotein cholesterol; BNP, brain natriuretic peptide.

other traditional indexes in predicting cardiovascular outcomes, and could be a sensitive parameter to mild HF. It could be utilized as a tool for risk stratification in CAD patients or incorporated into a prediction model to improve efficacy.

Limitations

There are certain limitations to our study. Firstly, the study involved a post hoc exploratory analysis on the basis of follow-up data from a single center. However, selection bias may have been avoided to some extent due to the consecutive enrolling strategy of a cross-sectional study. Secondly, the sample size was relatively small, and further analysis in patients with reduced LVEF was restricted. Thirdly, many patients were eliminated owing to dropout or lack of echocardiographic data, which could give rise to biased results.

Conclusions

EAS index was a powerful and independent predictor of MACE in patients with obstructive CAD. It exhibited superiority over other traditional indexes in predicting cardiovascular outcomes, especially in patients with preserved LVEF.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-109/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-109/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Guangdong Provincial People's Hospital (No. GDREC2017203H) and informed consent was provided by all individual participants.

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