Original Article

Relationship between the Severity of Coronary Artery Disease and Cardiovascular Risk Factors in Acute Coronary Syndrome: Based on Tehran Heart Center's Data Registry

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Abstract

Background: Acute coronary syndrome (ACS) is one of the main causes of mortality worldwide. We sought to evaluate the correlation between the severity of coronary artery disease (CAD) and conventional coronary artery risk factors in a large cohort of patients with ACS.

Methods: This study included all patients admitted to the coronary care unit with a diagnosis of ACS between 2003 and 2017. The patients were divided into 2 groups: 1) unstable angina and 2) myocardial infarction. The aims of this study were to evaluate the effects of the risk factors and extension of coronary artery stenosis in patients with ACS according to the Gensini score.

Results: Of a total 40 319 patients who presented with ACS, 18 862 patients (mean age =60.4±11.14 y, male: 67.2%) underwent conventional coronary angiography and met our criteria to enter the final analysis. The median of the Gensini score was 50 (25–88) in the study population. The multivariable analysis showed that age, sex, diabetes mellitus, hypertension, dyslipidemia, family history, cigarette smoking, opium consumption, and myocardial infarction increased the risk of positive Gensini scores. All the aforementioned risk factors, except cigarette smoking and opium consumption, increased the severity of stenosis in those with positive Gensini scores. The strongest relationship was seen vis-à-vis myocardial infarction, sex, and diabetes mellitus.

Conclusion: Our findings suggest that age, sex, diabetes mellitus, dyslipidemia, hypertension, family history, and myocardial infarction have significant effects on the severity of CAD. The obesity paradox in relation to CAD should be taken into consideration and needs further investigation in patients with ACS.

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Introduction

Acute coronary syndrome (ACS) is one of the most prevalent presentations of coronary artery disease (CAD) and the leading cause of death.[1-10] Also a notable cause of morbidity and mortality in the middle-aged population, ACS is defined as a spectrum ranging from unstable angina (UA) to myocardial infarction (MI).[11] Diagnosis is established based on clinical symptoms, electrocardiographic (ECG) features, and cardiac biomarkers.[12] The conventional risk factors of CAD are diabetes mellitus (DM), hypertension (HTN), smoking, dyslipidemia (DLP), family history, and obesity.[13] The distribution of treatment according to guidelines varies from medical treatment to revascularization.[12] Coronary angiography is used to assess the severity of CAD based on the Gensini score in many patients diagnosed with ACS. To our knowledge, the existing literature lacks studies on the correlation between the severity of CAD and conventional coronary artery risk factors; we, therefore, performed the present investigation to address this issue.

This historical cohort study is based on Tehran Heart Center's ACS Data Registry, which includes all patients admitted to our center with a diagnosis of ACS between August 2003 and July 2017. All patients who had ACS and underwent coronary angiography were enrolled in this study. Patients without confirmed diagnoses of ACS and missing hospital records were excluded from the study. The study population was stratified into 2 groups: 1) UA and 2) MI. The study protocol was approved by the Ethics Committee of the Tehran Heart Center and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

According to Tehran Heart Center's ACS Data Registry, trained general practitioners visited the patients and completed a datasheet compiling information on demographics, symptoms, major risk factors of CAD (DM, HTN, DLP, family history, cigarette smoking, opium consumption, and obesity), treatment modalities, laboratory and paraclinical results, and perioperative mortality. The data collection was conducted retrospectively, obviating the need for the patients' consent.

ACS was categorized into 2 main subtypes: UA and MI.[14]

UA may present in 1 of 3 ways: (i) as rest angina, defined as pain of characteristic nature and location occurring at rest and for prolonged periods (>20 min); (ii) new-onset angina, defined as a recent (2 mon) onset of moderate-to-severe angina (Canadian Cardiovascular Society grade II or III); or (iii) crescendo angina, defined as previous angina that progressively increases in severity and intensity, and at a lower threshold, over a short period of time.[15]

A combination of criteria is required to meet the diagnosis of acute MI. The criteria comprise the detection of an increase and/or decrease of a cardiac biomarker, preferably high-sensitivity cardiac troponin, with at least 1 value above the 99th percentile of the upper reference limit and at least 1 of the following: (1) symptoms of ischemia; (2) new or presumed new significant ST-T wave changes or left bundle branch block on 12-lead ECG; (3) development of pathological Q-waves on ECG; (4) imaging evidence of new or presumed new loss of viable myocardium or regional wall motion abnormalities; and (5) intracoronary thrombi detected on angiography or autopsy.[16]

HTN was defined as a minimum systolic blood pressure of 140 mmHg or a minimum diastolic blood pressure of 90 mm Hg or a history of antihypertensive therapy.[17, 18]

DM was defined as a fasting blood glucose level (measured twice) of equal to or greater than 126 mg/dL or the use of either oral hypoglycemic agents or insulin.[19]

DLP was defined as a minimum total cholesterol level of 240 mg/dL, a minimum triglyceride level of 200 mg/dL, or a high-density lipoprotein cholesterol level of less than 40 mg/dL in men and less than 50 mg/dL in women or a minimum low-density lipoprotein cholesterol level of 160 mg/dL or a history of prescribed lipid medications based on the National Cholesterol Education Program Adult Treatment Plan III.[20, 21]

The body mass index (BMI) was defined as the body weight in kilograms divided by the square of the body height in meters, and obesity[22] was defined as a BMI of equal to or greater than 30.0 kg/m².

With respect to smoking, the patients were divided into never smokers, former smokers (smoking cessation at least 3 months prior to admission), or current smokers based on their self-report.[23]

Opium consumption was self-reported in 12.2% of the cohort participants. Detailed data were obtained on the amount of use in "nokhod" (the local unit for opium use: ≈ 0.2 g), the duration and frequency of consumption, and the routes of administration.[24]

The Gensini score is a system based on the hypothesis drawing upon both stenosis scoring and vascular scoring. In this system, the sum of luminal stenosis in the coronary artery tree according to the location, number, and degree of luminal narrowing offers a quantitative estimation of the severity of CAD.[14, 25] A score of 0 indicates the absence of luminal stenosis.

The baseline demographic and clinical characteristics of the study variables were presented as frequencies and percentages for categorical variables and the mean±the standard deviation (SD) or the median with interquartile range25%–75% (IQR25%–75%) boundaries for continuous variables with normal and skewed distributions, respectively. Since the Gensini score data have highly skewed distributions with clumping at 0, we analyzed it by applying a 2-part model. In the first part, the Gensini score was divided into a binary variable, encompassing 0s and positive Gensini scores (Table 2). Then the logistic regression model was used to evaluate the effects of variables on the increase in the Gensini score. In the second part, after the discarding of 0 scores, a linear regression model was applied to assess the

effects of variables on the severity of the Gensini score. Due to the skewed distribution of the Gensini scores, the second part was analyzed on the logarithm of the Gensini scores. The data were analyzed by applying IBM SPSS Statistics for Windows, version 19.0 (Armonk, NY: IBM Corp).

Results

Of a total of 40 319 patients who were admitted to the coronary care unit with a diagnosis of ACS, 18 862 patients (mean age =60.4±11.14 y, male: 67.2%) underwent coronary angiography and were included in our final analysis. In this analysis, 9020 patients (47.8%) presented with UA and 6179 (32.8%) presented with MI. Table 1 demonstrates the frequency of risk factors among the study population. The prevalence of HTN, DLP, DM, and obesity among our cohort participants was 54.6%, 49.9%, 32.6%, and 28%, respectively. In the present study, 26% and 12.2% of the population were current cigarette smokers and opium consumers, respectively. Moreover, the lowest prevalence among the factors leading to an increased risk of positive Gensini scores belonged to family history of CAD.

The median of the Gensini score was 50 (25, 88) and was higher in men than women (53 vs 42, correspondingly). The distribution of the Gensini score was also higher in patients with DM (median=60, IQR25%–75%: 31.00 to 104.00) but was lower in patients with family history than male patients (median=48, IQR25%–75%: 24.00 to 87.00).

The univariate and multivariable effects (analysis) of the risk factors on the Gensini score are illustrated in Table 2. The univariate analysis of each independent variable demonstrated only its effect on the Gensini score as a dependent variable, while the multivariable analysis showed

not only the effects between a set of independent and dependent variables but also the relationship within each set of variables.

Table 1. Baseline characteristics of the study population*

Age (y)	60.40±11.14
Sex	
Male	12683 (67.2)
Female	6179 (32.8)
Types of ACS	
Unstable angina	9020 (47.8)
Myocardial infarction	9842 (52.2)
Obesity (BMI≥30)	4473 (28.0)
Diabetes mellitus	6135 (32.6)
Family history	1759 (9.5)
Dyslipidemia	9400 (49.9)
Cigarette smoking	4912 (26.0)
Hypertension,	10299 (54.6)
Opium consumption	2301 (12.2)

*Date are presented as mean±SD or n (%)
ACS, Acute coronary syndrome; BMI, Body mass index

In other words, the multivariable effect showed an adjusted effect of each variable considering all the variables together. Table 2 consists of 2 parts: the upper part depicts the evaluation of the effects of variables on the occurrence of positive Gensini scores (Gensini score 0 vs >0), and the lower part illustrates the assessment of the effects of variables on the increase in the Gensini scores, indicating the severity of coronary artery stenosis. The results revealed that age, sex, DM, HTN, DLP, family history, cigarette smoking, opium consumption, and MI increased the risk of positive Gensini scores. Moreover, age, sex, DM, HTN, DLP, family history, and MI augmented the severity of stenosis in patients with positive Gensini scores. The strongest relationships were seen with MI (β: 2.29, 95% CI: 2.19 to 2.39; P<0.001), sex (male, β: 0.34, 95% CI: 0.31 to 0.37; P<0.001), and

Table 2. Univariate and multivariable effects of the conventional risk factors of coronary artery disease on the Gensini score

Variables	Univariate			Multivariable				Univariate			Multivariable		
	OR*	95% CI**	P	OR	95% CI	P	β***	95% CI	P	β	95% CI	P
Age	1.06	1.05-1.07	<0.001	1.08	1.07-1.08	<0.001	0.01	0.01-0.01	<0.001	0.02	0.01-0.02	<0.001
Sex, male	2.93	2.55-3.36	<0.001	4.06	3.39-4.87	<0.001	0.24	0.21-0.27	<0.001	0.34	0.31-0.37	<0.001
Diabetes mellitus	2.28	1.92-2.72	<0.001	2.35	1.93-2.87	<0.001	0.22	0.19-0.25	<0.001	0.23	0.20-0.26	<0.001
Hypertension	1.46	1.27-1.67	<0.001	1.47	1.24-1.74	<0.001	0.05	0.02-0.08	<0.001	0.04	0.01-0.07	0.009
Dyslipidemia	1.60	1.39-1.84	<0.001	1.71	1.46-2.01	<0.001	0.08	0.05-0.11	<0.001	0.11	0.08-0.15	<0.001
Obesity	0.61	0.52-0.70	<0.001	0.84	0.71-0.99	0.034	-0.13	-0.17- -0.10	<0.001	-0.04	-0.07- -0.01	0.019
Family history	1.11	0.87-1.41	0.409	1.91	1.46-2.01	<0.001	-0.02	-0.07-0.02	0.334	0.11	0.06-0.16	<0.001
Cigarette smoking	1.86	1.55-2.23	<0.001	1.49	1.18-1.88	0.001	0.01	-0.02-0.04	0.652	-0.01	-0.04-0.03	0.752
Opium consumption	2.06	1.57-2.71	<0.001	1.42	1.02-1.96	0.036	0.04	0.00-0.08	0.67	0.03	-0.02-0.08	0.199
MI	3.88	3.31-4.56	<0.001	3.98	3.31-4.79	<0.001	0.41	0.39-0.44	<0.001	2.29	2.19-2.39	<0.001

*Odds ratio;
**Confidence interval;
***Beta (β) is the logarithm of the positive Gensini scores.
The Gensini score was analyzed through the application of a 2-part model. In the first part, the Gensini score was divided into a binary variable, consisting of 0s and positive Gensini scores. The outcome was a Gensini score of greater than 0 and was expressed in terms of odds ratios. In the second part, after the discarding of the 0 scores, a linear regression model was applied to assess the effects of variables on the severity of the Gensini scores. Due to the skewed distribution of the Gensini scores, the second part was analyzed on the logarithm of the Gensini scores and expressed in terms of beta (β).
MI, Myocardial infarction

DM (β: 0.23, 95% CI: 0.20 to 0.26; P<0.001), respectively. Whereas cigarette smoking (β: −0.01, 95% CI: −0.04 to 0.03; P=0.752) and opium consumption (β: 0.03, 95% CI: −0.02 to 0.08; P=0.199) had no significant effect on the increase in the Gensini score, obesity had a reverse effect on the score (β: −0.04, 95% CI: −0.07 to −0.01; P=0.019).

Discussion

Risk factors assist in the assessment of CAD severity based on the Gensini score in patients suffering from ACS. We evaluated the correlation between CAD severity and conventional CAD risk factors in this patient population. Our study is probably the first and largest one to utilize coronary angiography for the evaluation of CAD severity in terms of the Gensini score.

According to the results of the Reduction of Atherothrombosis for Continued Health (REACH) Registry, the mean age of Asian patients referred for coronary artery bypass grafting surgery was 64.7 years, as opposed to 70.1 years in North American patients.[26] Therefore, the mean age of our patients is lower than that of their Asian and North American counterparts. Mandegar et al[27] and Ostovan et al[28] reported the mean age of their patients to be 58.7 and 62.2 years, correspondingly, which is similar to our study findings.

Our study revealed that of all the various clinical predictors of the severity of CAD, male gender and MI affected the Gensini score the most significantly. We also found that the 2 risk factors of cigarette smoking and opium consumption had no significant correlation with angiographic severity. Additionally, there was a negative correlation between obesity and CAD severity.

It is known that men generally develop CVD at a younger age and have a higher propensity for CAD development than women. They are also more likely to develop severe CAD than age-matched women, even without presenting with MI. Consistently, we found that male gender exerted a significant influence on the severity of CAD and led to a prominent positive association with the Gensini score (OR: 4.06, 95% CI: 3.39 to 4.87; P<0.001).[29, 30]

Our results demonstrated that cigarette smoking exerted no significant effect on the Gensini score (P=0.752), similar to the smoker's paradox in a study by Masaki et al[31] on 6195 patients who underwent percutaneous coronary intervention for ACS in Japan. The authors attributed this finding to a higher comorbidity rate in nonsmoking patients and the different presentations of ACS in smokers.[31-33] Ostovan et al[28] studied 246 Iranian patients who underwent coronary artery bypass grafting in the city of Shiraz and demonstrated the prevalence of coronary risk factors in this group of patients in comparison with Asian and North American patients according to the data of the REACH Registry.[26] In the present study, the prevalence rates of all the risk factors are similar to those reported by Ostovan and colleagues which are lower than those reported in Asian and North American patients.

Zencirci et al[34] also demonstrated that the Gensini score had a high correlation with MI, which led to adverse events on follow-up. In our study, we also found that patients who presented with MI had a significantly higher correlation with a positive Gensini score than those who presented with UA.

Atherosclerosis accounts for one of the most common causes of microvascular and macrovascular complications, and DM has a strong association with atherosclerosis. Thus, DM is an established risk factor for CAD and is associated with an approximately twofold increase in the risk of ACS.[35, 36] Saleen et al[37] designed a study on the association between DM and CAD severity based on the Gensini score and demonstrated a significant association between the Gensini score and DM. Their finding is concordant with ours inasmuch as we detected that after male gender and MI, one of the most significant correlations was that between the Gensini score and DM.

In our assessments, we considered the obesity paradox and its association with the Gensini score to be independent of DM. Obesity is associated with a high global burden the world over.[17] Not only does obesity increase the risk of DM but also it is deemed a mortality risk factor in the general population.

Previous research has shown a lower median of the Gensini score in obese patients than nonobese patients.[38-41] This finding is in line with that in a meta-analysis of the obesity paradox in patients with ACS by Niedziela et al,[22] who reported that for a BMI range of 25 to 29.9 kg/m², the mortality was lower in the general population, while an obesity paradox might occur in patients with ACS or chronic diseases. A possible explanation for this inverse relationship is that the obese patients recruited were younger and the percentage of these obese patients decreased by aging, owing to a lower expected lifetime.[42] Nonetheless, it is worthy of note that in that meta-analysis, the obesity paradox persisted after adjustments were made for age.[23] Another explanation having been suggested for this enigma is that coronary angiography is done more frequently in obese patients.[43, 44] Our results do not chime in with this explanation. However, the obesity paradox was not observed in a study on 3469 Saudi patients with ACS by Mobeirek et al[45] and a study on 3686 Chinese patients admitted with CAD by Chai et al.[46] We, therefore, recommend that large-scale cohort studies on patients suffering from obesity be designed.

The main advantage of our study is that it is, to the best of our knowledge, the first and largest one to evaluate the severity of CAD based on the Gensini score via coronary angiography. Our study also has some noteworthy limitations, first and foremost among which is our inability to utilize anthropometric measures other than BMI such as the waist circumference or the waist/hip ratio for the assessment of

the relationship between obesity and the severity of CAD in ACS. Additionally, we had some missing and incomplete information, which is a problem inherent to other studies based on data registries.

Conclusion

In our study population, the coronary artery disease risk factors of age, sex, diabetes mellitus, hypertension, dyslipidemia, family history, and myocardial infarction, but not smoking and opium consumption, increased the Gensini score as a criterion for the severity of coronary artery disease. The obesity paradox should be taken into consideration in the assessment of coronary artery disease severity and warrants further research.

Acknowledgments

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