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Original Article

Evaluation of long-term mortality in patients with stable angina pectoris whose SYNTAX score was found to be zero in coronary angiography

Dogan Ilis, Cengiz Burak, Ahmet Karakurt

Department of Cardiology, Faculty of Medicine, Kafkas University, Kars, Turkey

Abstract

Aim: The number of diagnostic coronary angiography is increasing. Although previously thought that non-obstructive coronary artery disease (CAD) does not cause an increase in mortality risk, there is recently evidence that it increases mortality. In this study, we aimed to determine the mortality rates and possible predictors of all-cause death in long-term follow-up of patients who underwent coronary angiography (CAG) due to stable angina and whose SYNTAX score was zero including normal coronary arteries, minimal CAD or non-obstructive CAD, coronary slow flow, coronary artery aneurysms and ectasia.

Materials and Methods: This study included 1489 patients who underwent CAG due to stable angina pectoris. In-hospital and post-discharge follow-up data were obtained. Patients' CAG images were evaluated and SYNTAX scores were calculated using the website calculator.

Results: Among the 1489 patients, 64 (4.3%) all-cause deaths were observed during the 19 ± 1.1 months of follow up period. Although, no significant difference was observed between the 2 groups in terms of the presence of plaque in coronary arteries with a vessel diameter of ≤ 1.5 mm, the rate of patients with plaque in coronary arteries with a diameter of > 1.5 mm was significantly higher in the group of patients who died compared to the patients living (48 (75%) vs 842 (% 59.1), p = 0.011). The cumulative survival curve of the patients was obtained and in patients with coronary plaque in any of the coronary arteries with a vessel diameter of > 1.5 mm was significantly associated with worse survival.

Conclusion: There was increase in all-cause mortality in patients who underwent CAG due to stable angina and who have at least one non-obstructive lesion in the coronary arteries > 1.5 mm. Therefore, appropriate risk classification, life style changes and appropriate medical follow-up may be important in these patients.

Keywords: Mortality; Non-obstructive coronary artery disease; SYNTAX score

INTRODUCTION

Non-obstructive coronary artery disease (Non-CAD) is a clinical entity in which hemodynamically non-significant obstructions are observed in the coronary arteries. The prevalence of Non-CAD has been reported to be range from 40% to 60% in the elective coronary angiography (CAG) procedures (1,2). Some pathologic abnormalities have been suggested, such as endothelial dysfunction, microvascular dysfunction, and vasospasm, to better explain the underlying pathophysiologic mechanisms (3). Although it was previously thought that Non-CAD was not related with an increased mortality risk, recently there is an evidence that it has increased mortality, especially in some subgroups of patients (4).

The Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) is a systematic scoring system used to be determining the revascularization strategy by evaluating the severity, localization, and features of the lesions found in the CAG (5). In this score, if the coronary artery diameter is >1.5 mm and ≥ 50% diameter narrowing is present, the lesion is counted and scored. It is well-known that both percutaneous coronary intervention (PCI)- and coronary artery bypass grafting-related mortality and adverse cardiovascular outcomes are higher in patients with a high SYNTAX score (6). However, there is a limited data regarding mortality in patients with minimal or Non-CAD, which is also referred to as those with a SYNTAX score of zero.

In this study, we aimed to determine the long-term, all-cause mortality rates and possible predictors in patients who underwent CAG due to stable angina pectoris and

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Corresponding Author: Dogan Ilis, Department of Cardiology, Faculty of Medicine, Kafkas University, Kars, Turkey
E-mail: ilisdogan@hotmail.com

whose SYNTAX score was zero, such as those with normal coronary arteries, minimal CAD or Non-CAD, coronary slow-flow, ectatic/aneurysmatic coronary arteries.

MATERIALS and METHODS

Study population

This retrospectively designed study included 1489 stable angina pectoris patients who were admitted to the Department of Cardiology of Kafkas University between January 2017 and December 2018. All patients underwent CAG, and their SYNTAX score was found to be zero. All patients were over 18 years old and ischemic findings were shown with using non-invasive tests in most cases. We excluded the patients whose SYNTAX score was greater than zero and had a known history of CAD. In addition, patients with elevated troponin due to non-cardiac reasons after an index hospitalization and patients with plaque rupture or erosion or thrombus found in the CAG were not included. Acetylsalicylic acid and Statin treatments were given to the patients with non-critical stenosis in coronary angiography, if there were no contraindications. Beta blocker, calcium channel blocker and / or nitroglycerine treatment were initiated in patients with angina. In-hospital follow-up data were obtained from the medical files, and post-discharge follow-up data were obtained by either outpatients visits or contacting the patient or relatives by phone. For patients who could not be reached, the information was obtained from the National Statistical Institute and the Birth Records Registry to determine whether they were alive or dead. The present study protocol was reviewed and approved by the Kafkas University Ethics Committee (No:80576354-050-99/227) in accordance with the principles of Declaration of Helsinki.

Data collection and definitions

Hospital database and medical files were scanned and demographic characteristics and laboratory parameters of all patients were recorded. Patients' CAG images were evaluated by two experienced invasive cardiologists from the hospital electronic database and, the SYNTAX scores were calculated using a website calculator (http://www.syntaxscore.com/calculator/start). In the event of a disagreement, the opinion of a third invasive cardiologist was consulted. The SYNTAX score of zero defined as the absence of coronary lesion, which causes ≥ 50% reduction in the coronary artery luminal diameter of > 1.5 mm. The coronary slow flow phenomenon is defined as an delayed distal vascular opacification in the absence of severe epicardial coronary disease (7). Thrombolysis in myocardial infarction (TIMI) frame count (TFC) was used to determine coronary slow-flow as described by Gibson et al (8). For the left anterior descending artery, TFC was corrected by division by 1.7 and the diagnosis of coronary slow-flow was made according to the previous recommendation (8). Coronary arterial dominance was defined as the vessel gives rise to the posterior descending artery. If the coronary artery had an angle of 90 degrees or more or at least three angles of 45-90 degrees, it was accepted as the coronary tortuosity [5]. Coronary artery ectasia was defined as the enlargement of a coronary artery to 1.5 times or more than its adjacent normal coronary artery diameter (9). A myocardial bridge was described as one or more of the coronary arteries goes through the heart muscle instead of lying on its surface, and more than 50% narrowing of the vessel diameter in the CAG images during systole was accepted as a significant coronary myocardial bridge (10). Multiple microfistulas from the coronary artery to the left ventricle and fistulas <1.5 mm in diameter were defined as coronary microfistulas, fistulas ≥ 1.5 mm in diameter were defined as coronary macrofistulas (11).

Statistical analysis

SPSS 25.0 statistical package program (Statistical Package for the Social Sciences, version 25.0, SSPS Inc., Chicago, IL, USA) was used for the statistical analysis. The Kolmogorov–Smirnov test was used to evaluate the distribution of continuous variables. Results were expressed as n (%) for categorical variables and mean ± standard deviation for continuous variables with normal distribution. The variables without normal distribution were presented as median (interquartile range). Either the Chi-squared test or Fisher's exact test was used to compare the categorical data, continuous variables were compared with the Student's t test or the Mann–Whitney U test. Because our study was nonrandomized, we performed a fuzzy matching based on age, diabetes mellitus, hypertension, hyperlipidaemia, family history of CAD and smoking to balance patient's characteristics. The Kaplan–Meier method was used to compare the cumulative survival curves of patients with coronary lesion of less than 50% and the vessel diameter of >1.5 mm and those without it. A two-tailed p value of < 0.05 was accepted as statistically significant.

RESULTS

A total of 1489 patients who underwent CAG due to stabile angina pectoris were included in the study (mean age was 58±12, 53.1% of them were female). In the present study, a total of 64 deaths were observed during the 19±1.1 months of follow-up period. Patients who died during follow-up were older (68±12 vs 58±12, p <0.005). While the frequency of diabetes mellitus (19 (29.7%) vs 265 (18.6%), p = 0.027) was higher, the ratio of female gender was lower (23 (35.9%) vs 767 (53.8%), p = 0.005) in patients who died compared to those who survivored. There was no significant difference in other demographic features. When laboratory data of the patients were examined, white blood cell (WBC) count ($8.1x10^3$ / µL (6.4-10.2) vs 7.1 $x10^3$ / µL (5.9-8.4), p <0.005), C-reactive protein (CRP) (1.39 mg / dL (0.44-2.88) vs (0.32 mg / dL (0.15-0.67), p <0.005), urea (58±34 mg/dL vs 37±15 mg/dL, p <0.005) and creatinine levels (0.86mg/dL (0.68-1.14) vs 0.80 mg/dL (0.67-0.94)) were higher in patients who did not survive. Additionally, estimated glomerular filtration rate (eGFR) was significantly lower in patients who were

dead compared to those who lived (79 mg/min/1.73 m^2 (63-94) vs 93 mg/min/1.73 m2 (80-10^2), p <0.005). The demographic and laboratory data of the patients are given in Table 1.

Comparison of coronary angiography findings of two groups were given in Table 2. There was no significant difference between the groups in terms of right coronary artery (RCA) as the dominat coronary artery, coronary slow-flow, anomalies of the coronary origin, coronary tortiosity, coronary myocardial bridge, the presence of coronary macrofistula, ectasia and aneurysm. The frequency of coronary microfistula and localized retention of opaque agent were significantly higher in patients who died compared to those who lived (2 (3.1%) vs 7 (0.5%), p = 0.008, 10 (15.6%) vs 120 (8.4%), p = 0.046, respectively). Although no significant difference was observed between

Table 1. Demographic and laboratory data of all patients underwent coronary angiography due to angina pectoris

	All patients (n: 1489)	Survivors (n:1425)	Non-survivors (n:64)	p value
Age, years	58 ± 12	58 ± 12	68 ± 12	<0.005
Gender, woman,n(%)	790 (53.1)	767 (53.8)	23 (35.9)	0.005
Diabetes mellitus, n(%)	284 (19.1)	265 (18.6)	19 (29.7)	0.027
Hypertension,n(%)	542 (36.4)	520 (36.5)	22 (34.4)	0.731
Hyperlipidaemia, n(%)	383 (25.7)	361 (25.3)	22 (34.4)	0.106
Smoking status, n(%)	838 (56.3)	803 (56.4)	35 (54.7)	0.793
Family history of CAD, n (%)	348 (23.4)	336 (23.6)	12 (18.8)	0.372
Acetylsalicylic acid, n (%)	26 (1.7)	26 (1.8)	0 (0)	0.276
Statin, n (%)	297 (19.9)	286 (20.1)	11 (17.2)	0.572
B-Blockers,n (%)	97 (6.5)	96 (6.7)	1 (1.6)	0.101
ACEİ/ARB, n (%)	277 (18.6)	261 (18.3)	16 (25)	0.179
Haemoglobin, g/dL	14 ± 3	14 ± 3	14 ± 2	0.183
WBC, 10^3/µL	7.1 (5.9-8.5)	7.1 (5.9-8.4)	8.1 (6.4-10.2)	<0.005
Platelet count, 10^3/L	246 ± 69	246 ± 68	229 ± 92	0.042
Glucose, mg/dL	113 ± 41	112 ± 39	132 ± 73	0.021
Urea,mg/dL	38 ± 16	37 ± 15	58 ± 34	<0.005
Creatinine,mg/dL	0.80 (0.68-0.95)	0.80 (0.67-0.94)	0.86 (0.68-1.14)	0.026
eGFR, mg/dk/1.73 m^2	92 (80-102)	93 (80-102)	79 (63-94)	<0.005
Sodium, mmol/L	141 ± 34	141 ± 35	140 ± 4	0.200
Potassium,mmol/L	4.35 (4.06-4.62)	4.35 (4.06-4.61)	4.46 (4.01-4.69)	0.369
Total cholesterol (mg/dL)	188 ± 59	188 ± 58	167 ± 57	<0.005
LDL cholesterol (mg/dL)	112 (88-134)	112 (89-135)	92 (69-128)	0.015
HDL cholesterol (mg/dL)	46 ± 15	46 ± 15	42 ± 15	0.017
TG cholesterol (mg/dL)	126 (88-183)	127 (89-184)	97 (72-143)	<0.005
ALT (IU/L)	19 (14-27)	19 (14-27)	20 (15-43)	0.088
AST (IU/L)	19 (16-23)	19 (16-23)	21 (16-32)	0.049
C-Reactive protein (mg/dL)	0.33 (0.16-0.75)	0.32 (0.15-0.67)	1.39 (0.44-2.88)	<0.005

Abbreviations:CAD;Coronary Artery Disease,ACEI/ARB; Angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers,WBC; White blood cells,LDL;Low-density lipoprotein, HDL; High density lipoprotein, TG; Triglyceride,ALT; Alanine transaminase, AST; Aspartate transaminase, eGFR; Estimated glomerular filtration rate

the two groups in terms of the presence of plaque in coronary arteries with a vessel diameter of ≤ 1.5 mm, the rate of plaque presence in coronary arteries with a diameter of > 1.5 mm was significantly higher in the non-survivor group (48 (75%) vs 842 (% 59.1), p = 0.011).

Due to the presence of significant differences between two groups, we performed a fuzzy matching. In all, 64 well-matched patients were selected from both survivor and non-survivor group, and their angiographic datas were compared (Table 3 and 4). The number of patients with coronary plaque in a vessel diameter of > 1.5 mm was significantly higher in the non-survivor group (48 (75%) vs 28 (43.8%), p <0.005). Additionally, the number of patients with coronary ectasia and opaque retention were higher in the same group (5 (7.8%) vs 0 (0.0%), p = 0.023, 10 (15.6%) vs 3 (4.7), p = 0.041, respectively). There was no significant difference in terms of coronary microfistula between the groups.

The cumulative survival curve of the patients was given in Figure 1. Patients with a coronary plaque in the coronary arteries with a vessel diameter of > 1.5 mm had significantly higher deaths during the long-term follow-up.

Table 2. Anatomical and functional evaluation of patients' coronary angiography images

	All patients (n: 1489)		Survivors (n:1425)		Non-survivors (n:64)		p value
Normal coronary arteries , n (%)	558	(37.5)	543	(38.1)	15	(23.4)	0.018
Coronary domination RCA , n (%)	1242	(83.4)	1186	(83.2)	56	(87.5)	0.371
Coronary slow flow, n (%)	107	(7.2)	99	(6.9)	8	(12.5)	0.093
Coronary artery origin anomalies, n (%)	22	(1.5)	21	(1.5)	1	(1.6)	0.954
Proximal tortiosity, n (%)	92	(6.2)	88	(6.2)	4	(6.3)	0.981
Distal tortiosity, n (%)	779	(52.3)	742	(52.1)	37	(57.8)	0.368
Myocardial bridging, n (%)	55	(3.7)	52	(3.6)	3	(4.7)	0.667
Coronary plaque (diameter >1.5 mm), n (%)	890	(59.8)	842	(59.1)	48	(75)	0.011
Coronary plaque (diameter ≤ 1.5 mm), n (%)	22	(1.5)	21	(1.5)	1	(1.6)	0.954
Localized opaque retention, n (%)	130	(8.7)	120	(8.4)	10	(15.6)	0.046
Coronary artery fistula, macro, n (%)	5	(0.3)	5	(0.4)	0	(0)	0.635
Coronary artery fistula, micro, n (%)	9	(0.6)	7	(0.5)	2	(3.1)	0.008
Coronary ectasia, n (%)	54	(3.6)	49	(3.4)	5	(7.8)	0.067
Coronary aneurysm, n (%)	16	(1.1)	14	(1)	2	(3.1)	0.104

RCA; Right coronary artery

Table 3. Demographic data of the matched patient groups

	All patients (n: 128)		Survivors (n:64)		Non-survivors (n:64)		p value
Age, years	67 ± 12		66 ± 12		68 ± 12		0.297
Gender, woman, n (%)	32	(25)	9	(14.1)	23	(35.9)	<0.005
Diabetes mellitus, n (%)	38	(29.7)	19	(29.7)	19	(29.7)	1.0
Hypertension, n (%)	45	(35.2)	23	(35.6)	22	(34.4)	0.854
Hyperlipidemia, n (%)	35	(27.3)	13	(20.3)	22	(34.4)	0.075
Smoking, n (%)	78	(60.9)	43	(67.2)	35	(54.7)	0.149
Family history of CAD, n (%)	24	(18.8)	12	(18.8)	12	(18.8)	1.0
Acetylsalicylic acid, n (%)	1	(0.8)	1	(1.6)	0	(0)	0.317
Statin, n (%)	21	(16.4)	10	(15.6)	11	(17.2)	0.812
B-Blockers, n (%)	5	(3,9)	4	(6.3)	1	(1.6)	0.173
ACEİ/ARB, n (%)	25	(19.5)	9	(14.1)	16	(25)	0.120

CAD; Coronary Artery Disease, ACEI/ARB; Angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers

Table 4. Anatomical and functional evaluation of coronary angiography images of matched patient groups

	All patients (n: 128)		Survivors (n:64)		Non-survivors (n:64)		p value
Normal coronary arteries , n (%)	38	(29.7)	23	(35.9)	15	(23.4)	0.123
Coronary domination RCA , n (%)	103	(80.5)	47	(73.4)	56	(87.5)	0.050
Coronary slow flow, n (%)	15	(11.7)	7	(10.9)	8	(12.5)	0.784
Coronary artery origin anomalies, n (%)	2	(1.6)	1	(1.6)	1	(1.6)	1.0
Proximal tortiosity, n (%)	6	(4.7)	2	(3.1)	4	(6.3)	0.405
Distal tortiosity, n (%)	70	(54.7)	33	(51.6)	37	(57.8)	0.479
Myocardial bridging, n (%)	5	(3.9)	2	(3.1)	3	(4.7)	0.650
Coronary plaque (diameter >1.5 mm), n (%)	76	(59.4)	28	(43.8)	48	(75)	<0.005
Coronary plaque (diameter ≤ 1.5 mm), n (%)	3	(2.3)	2	(3.1)	1	(1.6)	0.561
Localized opaque retention, n (%)	13	(10.2)	3	(4.7)	10	(15.6)	0.041
Coronary artery fistula, macro, n (%)	0	(0.0)	0	(0.0)	0	(0)	1.0
Coronary artery fistula, micro, n (%)	3	(2.3)	1	(1.6)	2	(3.1)	0.561
Coronary ectasia, n (%)	5	(3.9)	0	(0.0)	5	(7.8)	0.023
Coronary aneurysm, n (%)	2	(1.6)	0	(0.0)	2	(3.1)	0.156

RCA; Right coronary artery

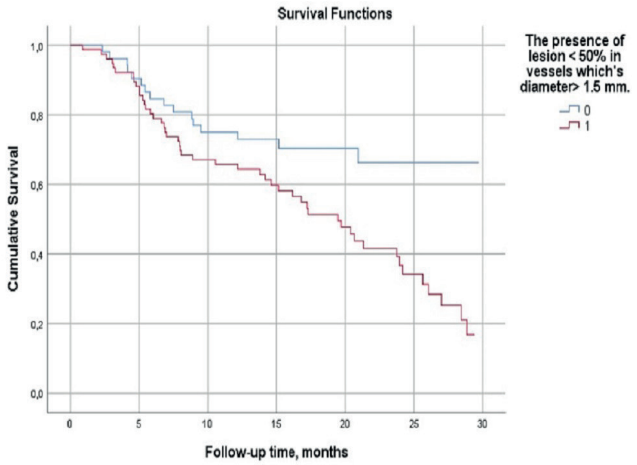

Figure 1. The cumulative survival curve of the patients. In patients with coronary plaque in any of the coronary arteries with a vessel diameter of > 1.5 mm was significantly associated with worse survival than those without

DISCUSSION

In the current literature, there is a contradictory and limited data regarding the relationship between the presence of Non-CAD and long-term mortality. The main result of our study was that the presence of lesion causing a diameter narrowing of <50% in any coronary vessel with a diameter of >1.5 mm in the CAG, that is also referred as Syntax score of zero, was found to be associated with increased all-cause long-term mortality.

In addition to being a known risk factor for CAD, advanced age was also shown to be associated with cardiovascular death and total mortality (12). As it is well-known, smoking also increases cardiovascular mortality (13). In our study, the mean age of the dead patients was significantly higher compared to those who lived, which was similar to the current literature. However, no difference was observed in terms of smoking. We considered that this might be due to the relatively small number of patients who died in addition to relatively short follow-up period. It has been shown that hypertension increases the risk of major atherosclerotic cardiovascular events, such as acute coronary syndrome, stroke, peripheral artery disease, and heart failure (14,15). In addition, hypertension has been shown to increase the incidence of post-myocardial infraction angina and sudden death (16). In our study, no difference was observed between the groups in terms of the frequency of hypertension, which might be due to the longer follow-up period is required for the emergence of hypertension-induced atherosclerotic events and their consequences.

CRP is a sensitive but non-specific marker of systemic inflammation. Although the role of CRP in the pathogenesis of CAD is less clear, increased CRP levels have been found to be associated with cardiovascular risk and obesity (17,18). Nevertheless, high sensitivity CRP (hs-CRP) showing chronic inflammation was shown to be associated with adverse cardiac events, and it was considered as an important risk factor in non-CAD (19,20). High WBC count is the immune system's response to both acute and chronic inflammation, and it is a non-specific inflammatory marker associated with irritating or toxic exposures, such as cigarette smoke (21,22). In the community-based studies, increased WBC has been shown to be associated an approximately 2-fold increase in total mortality and found to be associated with increased incidence of cardiovascular disease and mortality in people without known cardiovascular disease (23,24). In the previous studies, it has been shown that WBC is an independent risk factor for mortality even after the adjustment cardiovascular risk factors, and this effect competes with serum cholesterol, low density lipoprotein (LDL), and hypertension (25-29). In accordance with the literature, CRP and WBC were significantly higher in the group of patients who died compared to those who survived in our study. Urea and creatinine levels were also higher in patients who died. It can be said that inflammation plays an important role in the development of atherosclerosis, and inflammatory mediators may play a critical role in the atherosclerotic cascade starting from early endothelial cell dysfunction and continuing with the non-obstructive stenosis phase, all of which may be associated with an increased mortality. The other reasons for this was thought to be concomitant renal failure, age and other comorbidities.

Although it is not very clear, there are findings in the literature showing that coronary slow flow is a result of microvascular dysfunction (30). In histopathological studies involving patients with slow coronary flow, a reduction in lumen diameter, capillary, and endothelial damage has been demonstrated (30,31). The prevalence of coronary slow flow was found to be around 1-7% in patients underwent diagnostic CAG, and cardiac arrhythmia has been associated with cardiovascular events involving acute coronary syndrome (32,33). In our study, slow coronary flow was observed in 7.2% of patients and it was consistent with the literature. Although proportionally more slow coronary flow was observed in the group of patients who died, it was not statistically significant. The prevalence of coronary ectasia has been reported to be between 0.3-4.9% in patients undergoing CAG (34,35). In the previous studies, it has been shown that coronary ectasia is associated with ischemic heart disease, thrombus formation, vasospasm, coronary slow flow, even myocardial infarction, but the data regarding the coronary ectasia and mortality is limited (36,37). In our study, the prevalence of coronary ectasia was found to be 3.6%, and it was proportionally higher in the un-matched group of patients who did not survive. Similarly, the rate of patients with coronary ectasia was significantly higher in the matched group of those patients who died. Therefore, as supported by our study findings, the presence of coronary ectasia may be associated with all-cause mortality. This finding may be due to thrombus formation, myocardial infarction or lethal arrhythmias because of changing coronary flow hemodynamic. The number of patients with localized opaque retention in CAG

was higher in the non-survived group, and to the best of our knowledge, there is no data in the literature on this subject. The possible causes of this may be endothelial dysfunction and impaired flow hemodynamic, resulting in an increased risk of ACS and sudden death. However, more information is needed on this subject.

In the literature, patients with a SYNTAX score of zero are not considered as having CAD, and there is limited or conflicting data regarding mortality for patients. It had been showed that patients with chest pain and normal or Non-CAD had an excellent prognosis (38,39). However, in other studies conducted in a similar group of patients, including patients with Non-CAD and normal coronary arteries, have found an increased major adverse cardiac events and mortality in such patients (4,40). In our study, a lesion causing luminal diameter reduction <50% in the coronary vessels with a diameter of >1.5 mm was found to be associated with an elevated total mortality, and the all-cause mortality of such patients was higher than individuals with normal coronary arteries. There are several reasons to explain this result, one of which may be coronary microvascular dysfunction, which is known to be associated with major adverse cardiac events (41). Another reason may be acute myocardial infarction due to plaque rupture and sudden cardiac death due to lethal arrhythmias. In addition, the modification of the risk factors among these patients may be inadequate compared to patients with a significant CAD. Therefore, we believe that risk classification and appropriate medical treatment regimens may improve the prognosis of such patients during short- and long-term follow up.

Some limitations should be noted regarding to the present study. The study had a retrospective design and only all-cause mortality was evaluated. Therefore, the rate of cardiovascular mortality, which may be more specific, was unknown. The relatively short follow-up period may be another limitation. Although some well-known risk factors have been evaluated in the study, some unmeasured risk factors might have affected our results. Due to the retrospective nature of the study, objective measurements for microvascular dysfunction were not evaluated. Therefore, our results need to be supported by prospective, long-term study results.

CONCLUSION

In the present study, we observed an increase in all-cause mortality in patients who underwent CAG due to stable angina pectoris and had at least one lesion that did not cause a significant obstruction in the coronary arteries. Therefore, appropriate risk classification, life style changes, and appropriate medical follow-up are needed for such patients.

Conflict of interest : The authors declare that they have no competing interest.

Financial Disclosure: There are no financial supports.

Ethical approval: The present study protocol was reviewed and approved by the Kafkas University Ethics Committee (No:80576354-050-99/227) in accordance with the principles of Declaration of Helsinki.

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