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Clinical Significance of Coronary Artery Tortuosity in Chronic Coronary Syndrome and Stable Angina: Insights from Gensini Scores

Kronik Koroner Sendrom ve Stabil Angina'da Koroner Arter Kıvrımlılığının Klinik Önemi: Gensini Skorlarından Elde Edilen Görüşler

ABSTRACT

Objective: This study investigated the clinical significance of coronary artery tortuosity (CAT) in chronic coronary syndrome (CCS) using Gensini scores.

Method: This retrospective single-center study involved 388 patients undergoing coronary angiography for chest pain, excluding those with acute coronary syndromes or prior coronary interventions. Demographic, clinical, and angiographic data were collected and categorized based on the presence or absence of CAT.

Results: Analysis of 388 patients revealed that CAT was associated with older age ($P < 0.001$), female gender ($P < 0.001$), lower rates of smoking (19.3% vs. 29.6%, $P = 0.025$), and hypertension (53.5% vs. 38.7%, $P = 0.05$). There was a slightly higher, nearly significant, prevalence of diabetes in the CAT group (22.8% vs. 14.5%, $P = 0.051$). Furthermore, CAT correlated with diastolic dysfunction ($P = 0.04$) and was inversely related to the severity of coronary atherosclerosis, as indicated by lower Gensini scores correlating with higher CAT scores ($P = 0.039$ and $P = 0.049$, respectively). Univariate analysis confirmed CAT's association with older age ($P < 0.001$), female gender ($P < 0.001$), hypertension ($P = 0.004$), diabetes ($P = 0.039$), diastolic dysfunction ($P = 0.003$), and Gensini score ($P = 0.012$). Multivariate analysis further identified significant correlations with age ($P = 0.001$), female gender ($P < 0.001$), and Gensini score ($P = 0.049$).

Conclusion: Our findings indicate that older age and female gender predict presence of CAT in CCS patients. The lower Gensini scores associated with CAT may possibly be due to a reduced atherosclerotic plaque burden in these patients. Further research into this relationship could inform the development of treatment and management strategies for coronary atherosclerosis.

Keywords: Chronic coronary syndrome, coronary artery tortuosity, Gensini score

ÖZET

Amaç: Bu çalışmada, kronik koroner sendromda (KKS), Gensini skorları kullanılarak, koroner arter kıvrımlılığının (KAK) klinik önemi araştırılmıştır.

Yöntem: Retrospektif, tek merkezli çalışmaya kliniğimizde göğüs ağrısı nedeniyle koroner anjiyografi (KAG) uyguladığımız 388 hasta, akut koroner sendromu (AKS) olanlar ve önceden perkütan koroner girişim öyküsü olanlar dışlandıktan sonra dahil edildi. Hastalar KAK olanlar ve olmayanlar olarak iki gruba ayrıldı.

Bulgular: Çalışmaya alınan 388 hastanın analizi, KAK'ın ileri yaş ($P < 0,001$), kadın cinsiyet ($P < 0,001$), daha az sigara içme (%19,3'e karşı %29,6, $P = 0,025$) ve hipertansiyon (%53,5'e karşı %38,7, $P = 0,05$) ile ilişkili olduğunu gösterdi. KAK grubunda diyabetin biraz daha yüksek, sınırda anlamlı bir yaygınlığı vardı (%22,8'e karşı %14,5, $P = 0,051$). KAK ayrıca, diyastolik disfonksiyonla ($P = 0,04$), daha düşük Gensini skorları ve daha yüksek KAK skorlarıyla ilişkili olmakla birlikte koroner ateroskleroz şiddetiyle ters orantılıydı ($P = 0,039$; $P = 0,049$). Tek değişkenli analizler, KAK ile ileri yaş ($P < 0,001$), kadın cinsiyet ($P < 0,001$), hipertansiyon ($P = 0,004$), diyabet ($P = 0,039$), diyastolik disfonksiyon ($P = 0,003$) ve Gensini skoru ($P = 0,012$) arasında anlamlı korelasyonlar gösterdi. Çok değişkenli analizlerde, ileri yaş ($P = 0,001$), kadın cinsiyet ($P < 0,001$) ve Gensini skoru ($P = 0,049$) KAK ile anlamlı ilişkili bulundu.

Sonuç: Çalışmamızda, ileri yaş ve kadın cinsiyetin KKS'da KAK gelişimi için önemli belirleyiciler olduğu gösterilmiştir. KAK ile ilişkili düşük Gensini skorlarının muhtemelen bu hastalarda aterosklerotik plak yükünün daha az olmasından kaynaklanıyor olabilir. Bu ilişkinin daha ileri çalışmalarla araştırılması, koroner ateroskleroz için tedavi ve yönetim stratejilerinin geliştirilmesine yardımcı olabilir.

Anahtar Kelimeler: Kronik koroner sendrom, koroner arter kıvrımlılığı, Gensini skoru

ORIGINAL ARTICLE
KLİNİK ÇALIŞMA

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Coronary artery tortuosity (CAT) is usually an incidental finding in coronary angiography (CAG). Coronary artery tortuosity may be considered an anatomical variant in which the affected coronary vessels exhibit helical coils or consecutive curvatures.[1]

Aging, smoking, and hypertension are probable risk factors for tortuosity in coronary, femoral, cerebral, and carotid arteries; however, the primary risk factors for coronary artery tortuosity remain unknown. The impact of this phenomenon on cardiac events in coronary artery disease (CAD) is not well understood. Even though severe CAT with normal coronary arteries has been shown to correlate with myocardial perfusion defects, its role in development of angina is unclear.[2-5] Even while severe tortuosity is frequently regarded as benign and asymptomatic, it can cause myocardial ischemia by lowering coronary perfusion pressure.[6,7]

The pathophysiology of CAT is not fully elucidated; however, it is thought to involve elastin, a crucial extracellular matrix component that maintains arterial wall elasticity and stability.[8] Degeneration of elastin may weaken the arterial wall, leading to CAT.[9] Coronary artery tortuosity without coronary artery obstruction or atherosclerosis can cause angina pectoris during physical activity or exercise testing.[10] It is associated with chronic stable angina, reversible myocardial perfusion defects, subclinical atherosclerosis, and increased coronary artery calcium (CAC) scores, even in the absence of significant obstructive lesions.[11]

Chronic Coronary Syndrome and Stable Angina

Stable angina, resulting from an imbalance between myocardial oxygen demand and coronary blood flow, is often but not always associated with obstructive CAD. Angina is considered "chronic" and "stable" when symptoms persist for at least two months without changes in severity, nature, or precipitating factors. The dynamic process of CAD leads to different clinical presentations classified as either acute coronary syndrome (ACS) or Chronic Coronary Syndrome (CCS). Notably, there is no universal definition of angina pectoris; the term refers to both typical chest pain resulting from myocardial ischemia and a syndrome involving chest pain, myocardial ischemia, and obstructive atherosclerotic CAD.[12,13]

The aim of this study was to investigate the relationship between CAD and CAT using Gensini scores as a measure of CAD severity in patients with CCS/stable angina who underwent CAG. Although the definition of CCS has a broader perspective, CCS and stable angina were used synonymously in the present study. It should be noted that stable angina, which occurs as a clinical consequence of CCS, leads to CAG in some patients who do not respond to drug therapy or have significant ischemia confirmed by myocardial perfusion scintigraphy. Thus, we hope to provide pragmatic information for clinicians to develop management strategies for CCS/stable angina.

ABBREVIATIONS

ACS	Acute coronary syndrome
CAD	Coronary artery disease
CAG	Coronary angiography
CAT	Coronary artery tortuosity
CCS	Chronic coronary syndrome

Materials and Methods

This study was conducted according to the ethical standards defined in the Declaration of Helsinki, which was revised in 2013. Ethical approval for this study was obtained from the Ethics Committee of Necmettin Erbakan University (Approval Number: 1456-7952-050/633, Date: 09.03.2018). Prior to initiating the project, approval was sought from our local ethics committee within the hospital, where it was decided to ensure universal compliance with international ethical guidelines for patient selection and data analysis. Informed consent was not required due to the retrospective design of the study. The funders had no role in the study design, data collection and analysis, publication decisions, or manuscript preparation. This research thus demonstrated a commitment to upholding professional ethics while ensuring participant safety.

As part of the retrospective study design, no interventions or treatments were directly administered to the participants. This study analyzed patient records from our hospital's cardiology clinic from 2016 to 2017 to assess the prevalence and severity of tortuosity in the coronary arteries of individuals who presented with chest pain. The primary objective of this study was to explore the relationship between CAT and various cardiovascular conditions while maintaining unchanged patient care protocols. Demographic data, clinical history, and angiographic findings were collected to examine the potential effects of established cardiovascular treatment methods.

The study population included all patients who visited our cardiology clinic due to chest pain between 2016 and 2017 and underwent CAG. Among these patients, those followed for CCS and stable angina pectoris and who underwent planned CAG due to inadequate response to treatment or persistent anginal symptoms constituted our target population. Additionally, myocardial perfusion scintigraphy was used to confirm significant ischemia in some patients. Between 2016 and 2017, 1,227 patients who underwent CAG for chest pain in our hospital were narrowed down to a consecutive inclusion of 388 patients after the meticulous application of strict exclusion criteria. Exclusions included patients with acute coronary syndromes, unstable angina pectoris, non-ST elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), sudden death from cardiac causes, coronary artery bypass surgery (CABG), and those who had undergone prior percutaneous coronary intervention (PCI). These exclusions aimed to ensure that no confounding factors influenced the results, allowing for a focused assessment of CAT in a well-defined patient group. All data were meticulously collected to enrich our dataset, including demographic characteristics, laboratory parameters, and echocardiography findings (GE Healthcare, Vivid S6 echocardiography). For statistical analysis, the study population was divided into two groups: those with CAT and those without.

Definitions of Tortuosity: A main epicardial coronary artery with a diameter ≥ 2 mm was considered tortuous if it exhibited at least three successive curvatures, each ranging from 90° to 180° to be (Figure 1). A main epicardial coronary artery with a diameter ≥ 2 mm and two consecutive 180° bends was classified as having severe tortuosity (Figure 1). The main epicardial coronary artery

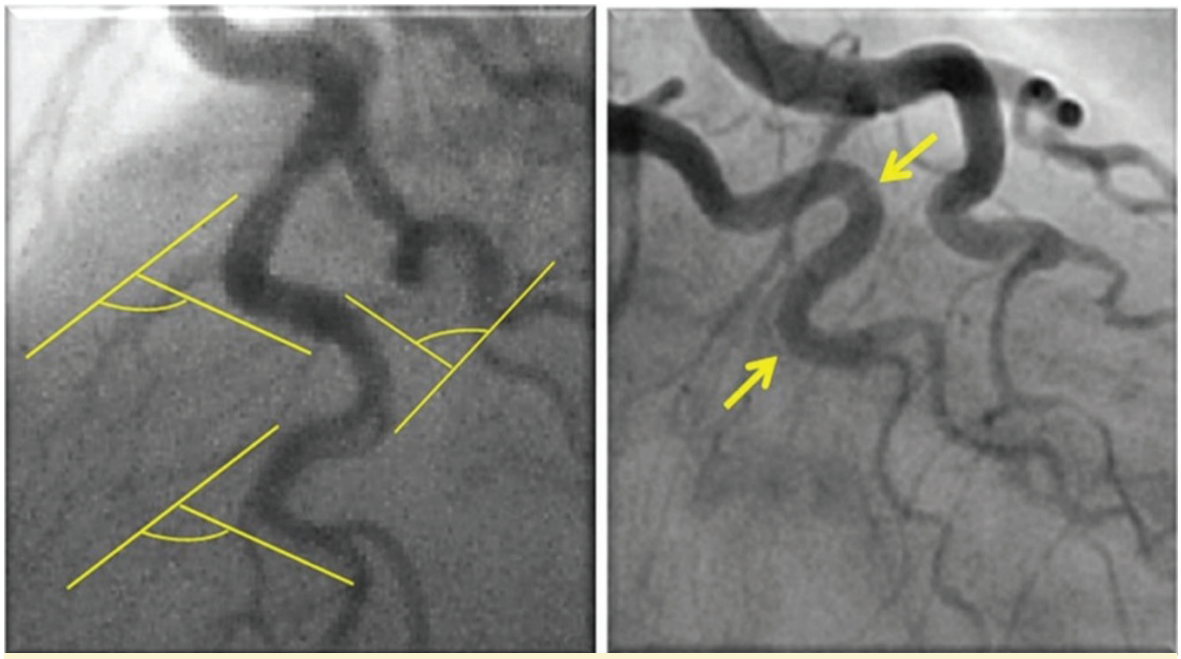

Figure 1. Definition of tortuosity. Left: Example of tortuosity in the left anterior descending coronary artery. Right: Example of severe tortuosity in the left circumflex coronary artery (*).
*Eleid MF, Guddeti RR, Tweet MS, et al. Coronary artery tortuosity in spontaneous coronary artery dissection: angiographic characteristics and clinical implications. *Circ Cardiovasc Interv*. 2014;7(5):656-662.

was considered to have mild tortuosity if it exhibited three consecutive curvatures of 45°-90° with a diameter ≥ 2 mm or three consecutive curvatures of 90°-180° with a diameter < 2 mm. The tortuosity score was determined by adding the scores for each major epicardial coronary artery (left anterior descending artery [LAD], left circumflex artery [LCX], and right coronary artery [RCA]), where 0 indicates no tortuosity, 1 indicates mild tortuosity, 2 indicates tortuosity, and 3 indicates severe tortuosity.[14,15] Patients who met these criteria and whose CAT scores were evaluated by at least two participating cardiologists were included in the study. Based on the presence of coronary tortuosity, the patients were divided into two groups: those with and those without CAT (Figure 1).

Echocardiography: Echocardiographic images of all patients were evaluated using conventional and M-mode echocardiography (GE Healthcare, Vivid S6 Echocardiography). Simpson's method was used to calculate the left ventricular ejection fraction (EF) from the same view. The apical four-chamber image was used to measure the peak mitral inflow E and A velocity waves on pulsed Doppler, the peak systolic and diastolic e' and a' velocities on tissue Doppler imaging at the lateral mitral annulus, and to determine the E/A ratio. A mitral E/A ratio of ≤ 0.8 was interpreted as indicative of diastolic dysfunction.[16] For this retrospective study, we relied on echocardiography reports performed as described and recorded in our hospital database.

Angiographic Assessments

All coronary angiograms were obtained using conventional techniques with either the femoral or radial artery approach, utilizing a Siemens radiographic unit (Siemens Healthcare, Germany) filming at 15 frames per second. Two cardiologists interpreted the images. Coronary anomalies other than coronary atherosclerosis, such as slow flow, muscle bridging, and ectasia, were recorded, and their relationship with CAT was evaluated.

The Gensini Scoring System used for quantifying the severity of CAD. Gensini scores the percentage of stenosis on a scale from 0 to 32, with higher scores indicating more severe disease.[17] The scores were calculated using quantitative coronary analysis (QCA) and visual estimation of stenosis severity.[17] For stenosis severity, 1 point was assigned for 1-25% stenosis, 2 points for 26-50%, 4 points for 51-75%, 8 points for 76-90%, 16 points for 91-99%, and 32 points for total occlusion (100%). After that, a factor reflecting the significance of the lesion's location within the coronary circulation is multiplied by each lesion score: 5 for the left main coronary artery, 2.5 for the proximal segment of the left anterior descending coronary artery, 1.5 for the mid-segment of the left anterior descending coronary artery, 1.0 for the right coronary artery, the distal segment of the left anterior descending coronary artery, the posterolateral artery, and the obtuse marginal artery, and 0.5 for other segments.[18] Patients were divided into two groups based on their Gensini scores: mild atherosclerosis (< 20 points) and severe atherosclerosis (> 20 points). The relationship between these groups and CAT was statistically evaluated.

Statistical Analysis

The data were analyzed to assess whether CAT is related to cardiovascular diseases, including associated risk factors. Continuous variables were reported as mean ± standard deviation or as median, minimum, and maximum values, while categorical variables were summarized as frequencies and percentages. The normality of distributions was assessed by testing whether the distributions were Gaussian using the Shapiro-Wilk, Anderson-

Table 1. Descriptive Statistics of Demographic and Clinical Characteristics of Patients and Comparison of Patients with and without Tortuosity

	Overall (n = 388)	Tortuosity (-) (n = 186)	Tortuosity (+) (n = 202)	*P*
Age, years[f]	57.7 ± 12.1	54.1 ± 12.2	61.0 ± 11.0	**<0.001****
Gender[J]				
Female	215 (55.4)	74 (39.8)	141 (69.8)	**<0.001***
Male	173 (44.6)	112 (60.2)	61 (30.2)	
Smoking Status, (%)[J]	94 (24.2)	55 (29.6)	39 (19.3)	**0.025***
Hypertension, (%)[J]	180 (46.4)	72 (38.7)	108 (53.5)	**0.005***
Diabetes, (%)[J]	73 (18.8)	27 (14.5)	46 (22.8)	0.051*
Hyperlipidemia, (%)[J]	179 (46.1)	85 (45.7)	94 (46.5)	0.950*
Coronary Atherosclerosis, (%)[J]	166 (42.8)	75 (40.3)	91 (45.0)	0.402*
Thyroid Dysfunction, (%)[J]				
No	348 (89.7)	171 (91.9)	177 (87.6)	0.241*
Hypothyroidism	20 (5.2)	6 (3.2)	14 (6.9)	
Hyperthyroidism	20 (5.2)	9 (4.8)	11 (5.4)	

[J], n (%); [f], Mean ± Standard Deviation; *Pearson Chi-Square, Fisher's Exact, or Fisher-Freeman-Halton test; **Independent Samples t-test.

Darling, and Kolmogorov-Smirnov tests. For categorical variables, where appropriate, Pearson chi-squared, Fisher's exact, and Fisher-Freeman-Halton tests were employed, as well as independent samples t-test and Mann-Whitney U test for continuous variables, depending on their skewness.

Linear regression was used to develop three models to determine risk factors: first, the Gensini score prediction model; second, a binary logistic regression analysis to predict the Gensini score as a dichotomous outcome (0-20 versus greater than 20); and third, a logistic regression analysis with backward elimination to determine predictors of the presence or absence of any tortuosity, including variables such as age, sex, smoking status, hypertension, diabetes mellitus, lipid levels, and inflammatory markers. The statistical analyses were conducted using Jamovi Version 2.3.28, (The Jamovi Project 2023, Computer Software, Sydney, Australia) and JASP Version 0.17.3, (JASP Team 2023, Computer Software, University of Amsterdam, Amsterdam, Netherlands). All statistical analyses were performed at a $P < 0.05$ significance level to ensure validity in assessing relationships between CAT and CAD indicators, such as risk factor profiles.

Results

In the analysis of the 388 patients included in the study, descriptive statistics showed that CAT was associated with older age ($P < 0.01$), female gender ($P < 0.01$), lower rates of smoking (19.3% vs. 29.6%, $P = 0.025$), and hypertension (53.5% vs. 38.7%, $P = 0.05$). Diabetes mellitus had a higher but borderline significant prevalence in the CAT group (22.8% vs. 14.5%, $P = 0.051$). Coronary artery tortuosity was not significantly associated with CAD, hyperlipidemia, or thyroid dysfunction ($P > 0.05$). These findings suggest that advanced age, female gender, and hypertension may be directly associated with CAT formation in patients with CCS and stable angina (Table 1).

When differences in hematologic and biochemical parameters were examined, fasting blood glucose (105.0 vs. 101.0 mg/dL, $P = 0.045$), urea (33.0 vs. 29.0 mg/dL, $P < 0.001$), uric acid (4.9 vs. 4.8 mg/dL, $P = 0.023$), high-density lipoprotein (HDL) cholesterol (47.0 vs. 43.5 mg/dL, $P < 0.001$), and red cell distribution width (14.4 vs. 13.7, $P = 0.001$) were significantly higher, while a more significant decrease was observed in red blood cell count (4.8 vs. 5.0, $P < 0.01$), hemoglobin (13.5 vs. 14.4, $P < 0.001$), lymphocytes (2.0 vs. 2.3, $P = 0.003$), and monocytes (0.5 vs. 0.6, $P = 0.002$) in relation to CAT formation. The significant yet mostly within-normal-limits associations between biochemical and hematologic values and CAT reflect the unique characteristics of the individuals included in the study. Therefore, it may not always be appropriate to directly associate these significant associations with the presence or pathophysiology of CAT. These statistics suggest unique characteristics and clues for patients in the CAT group. Some of these findings include higher urea and uric acid levels in the CAT group, while lymphocyte and monocyte levels were lower (Table 2).

When echocardiography and Gensini scores were analyzed in the CAT and non-CAT groups, no significant difference was observed in EF values between the two groups. There was no significant relationship between CAT and non-atherosclerotic causes of coronary ischemia, such as coronary slow flow, muscle bridging, or ectasia. However, a significant relationship was found between echocardiographic diastolic dysfunction and patients in the CAT group ($P = 0.004$). Additionally, there was a significant relationship between patients in the CAT group and Gensini scores indicating mild atherosclerosis ($P = 0.039$), with lower Gensini scores significantly associated with higher CAT scores ($P = 0.049$) (Table 3). The ejection fraction was 60% and above in 343 (88.4%) patients, between 50-60% in 33 (8.5%) patients, between 40-50% in nine

Table 2. Comparison of Hematological and Biochemical Parameters in Patients with and without Tortuosity

	Overall (n = 388)	Tortuosity (-) (n = 186)	Tortuosity (+) (n = 202)	*P**
Fasting Blood Glucose, mg/dL§	103.0 [62.0 – 483.0]	101.0 [69.0 – 350.0]	105.0 [62.0 – 483.0]	**0.045**
Urea, mg/dL§	31.0 [11.0 – 78.0]	29.0 [11.0 – 78.0]	33.0 [16.0 – 74.0]	**<0.001**
Creatinine, mg/dL§	0.9 [0.5 – 1.8]	0.9 [0.5 – 1.8]	0.9 [0.5 – 1.8]	0.154
Uric Acid, mg/dL§	4.9 [2.5 – 10.8]	4.8 [2.8 – 9.1]	4.9 [2.5 – 10.8]	**0.023**
Total Bilirubin, mg/dL§	0.4 [0.1 – 1.7]	0.4 [0.2 – 1.6]	0.4 [0.1 – 1.7]	0.671
Direct Bilirubin, mg/dL§	0.1 [0.0 – 0.9]	0.1 [0.0 – 0.9]	0.1 [0.0 – 0.5]	0.091
Indirect Bilirubin, mg/dL§	0.4 [0.0 – 1.4]	0.4 [0.1 – 1.4]	0.4 [0.0 – 1.4]	0.355
AST (Aspartate aminotransferase), U/L§	22.0 [8.0 – 107.0]	22.0 [8.0 – 63.0]	22.0 [11.0 – 107.0]	0.815
ALT (Alanine aminotransferase), U/L§	18.0 [6.0 – 112.0]	19.0 [6.0 – 99.0]	17.0 [7.0 – 112.0]	0.113
Thyroid Stimulating Hormone, mU/L§	1.4 [0.0 – 41.0]	1.4 [0.0 – 40.9]	1.4 [0.2 – 41.0]	0.538
Thyroxine (T4), ng/L§	1.1 [0.4 – 3.4]	1.2 [0.4 – 3.4]	1.1 [0.5 – 2.9]	0.362
Total Cholesterol, mg/dL§	190.0 [70.0 – 367.0]	188.5 [112.0 – 367.0]	193.0 [70.0 – 305.0]	0.307
Low-Density Lipoprotein, mg/dL§	111.0 [20.0 – 318.0]	109.9 [52.0 – 318.0]	111.7 [20.0 – 212.8]	0.932
Triglycerides, mg/dL§	136.0 [39.0 – 718.0]	136.5 [44.0 – 399.0]	136.0 [39.0 – 718.0]	0.446
High-Density Lipoprotein, mg/dL§	45.0 [24.0 – 84.0]	43.5 [24.0 – 71.0]	47.0 [25.0 – 84.0]	**<0.001**
Troponin, ng/L§	0.0 [0.0 – 50.0]	0.0 [0.0 – 50.0]	0.0 [0.0 – 17.4]	0.446
Creatine Kinase MB, µg/L§	13.0 [4.0 – 80.0]	13.0 [5.0 – 78.0]	12.8 [4.0 – 80.0]	0.750
C-Reactive Protein, mg/dL§	3.0 [0.1 – 111.0]	3.0 [0.1 – 111.0]	3.0 [0.2 – 100.0]	0.488
Red Blood Cells, $x10^6$/µL§	4.9 [3.0 – 7.7]	5.0 [3.3 – 7.2]	4.8 [3.0 – 7.7]	**<0.001**
White Blood Cells, $x10^3$/µL§	7.3 [3.7 – 21.7]	7.5 [3.8 – 21.7]	7.0 [3.7 – 15.8]	**0.005**
Hemoglobin, g/dl§	13.8 [8.3 – 18.3]	14.4 [9.8 – 18.3]	13.5 [8.3 – 17.7]	**<0.001**
Neutrophils, $x10^3$/µL§	4.3 [1.6 – 19.4]	4.5 [1.6 – 19.4]	4.2 [1.6 – 13.2]	0.059
Lymphocytes, $x10^3$/µL§	2.1 [0.4 – 5.1]	2.3 [0.6 – 4.5]	2.0 [0.4 – 5.1]	**0.003**
Platelets, $x10^3$/µL§	242.0 [103.4 – 516.0]	230.5 [103.4 – 407.0]	254.0 [104.0 – 516.0]	0.075
Monocytes, $x10^3$/µL§	0.6 [0.0 – 1.4]	0.6 [0.0 – 1.2]	0.5 [0.1 – 1.4]	**0.002**
Eosinophils, $x10^3$/µL§	0.1 [0.0 – 1.0]	0.2 [0.0 – 1.0]	0.1 [0.0 – 0.8]	0.142
Mean Platelet Volume, fL§	9.9 [7.2 – 13.6]	10.0 [7.2 – 13.6]	9.9 [7.2 – 12.5]	0.736
Red Cell Distribution Width, fL§	14.0 [10.2 – 23.3]	13.7 [10.5 – 21.9]	14.4 [10.2 – 23.3]	**0.001**

§, Median [Min-Max]; *, Mann-Whitney U test.

(2.3%) patients, between 30-40% in two (0.5%) patients, and below 30% in one (0.3%) patient. Diastolic dysfunction was observed in 91 (23.5%) patients, slow coronary flow in 36 (9.3%) patients, coronary ectasia in 30 (7.7%) patients, and myocardial muscle bridging in five (1.3%) patients. Among the 202 patients with tortuosity, 122 (60.4%) had mild tortuosity, 43 (21.3%) had moderate tortuosity, and 37 (18.3%) had a severe tortuosity index. According to the Gensini score, 377 (97.2%) patients were classified as low risk, five (1.3%) as moderate risk, and six (1.5%) as high risk for atherosclerosis. These findings highlight the importance of the association between CAT and echocardiographic diastolic dysfunction and suggest that the presence of CAT is associated with lower atherosclerotic risk scores (Table 3). In other words, CAT is related to diastolic dysfunction and it may be linked to less severe coronary atherosclerosis. It may be useful to investigate the lower atherosclerotic plaque burden with CAT in terms of coronary flow dynamics and the pathophysiology of atherosclerosis.

The univariate and multivariate analyses presented in Table 4 emphasize that older age and female gender are strong risk factors for CAT formation. Accordingly, men have a 70% lower risk of developing CAT than women (Adjusted Odds Ratio [OR]: 0.30, 95% Confidence Interval [CI]: 0.16-0.59, $P < 0.001$). Notably, older age, female gender, and hypertension are important risk factors for the development of CAT. Univariate and multivariate analyses also confirmed that lower Gensini scores were significantly associated with CAT ($P = 0.012$ and $P = 0.049$, respectively). This finding demonstrates that atherosclerotic plaque severity and burden were lower in the CAT group within the study population.

Table 3. Descriptive Statistics of Echocardiography (ECO) Findings and Gensini Scores with Comparisons in Patients with and without Tortuosity

	Overall (n = 388)	Tortuosity (-) (n = 186)	Tortuosity (+) (n = 202)	*P*
Echocardiography EF[J]				
EF ≥ 60%	343 (88.4)	171 (91.9)	172 (85.1)	0.078*
EF 50-60%	33 (8.5)	11 (5.9)	22 (10.9)	
EF 40-50%	9 (2.3)	2 (1.1)	7 (3.5)	
EF 30-40%	2 (0.5)	1 (0.5)	1 (0.5)	
EF < 30%	1 (0.3)	1 (0.5)	0 (0.0)	
Diastolic Dysfunction, (%)[J]	91 (23.5)	31 (16.7)	60 (29.7)	**0.004***
Tortuosity Intensity[J]				
Mild	122 (60.4)	0 (0)	122 (60.4)	--
Moderate	43 (21.3)	0 (0)	43 (21.3)	
Severe	37 (18.3)	0 (0)	37 (18.3)	
Coronary Slow Flow, (%)[J]	36 (9.3)	20 (10.8)	16 (7.9)	0.432*
Coronary Ectasia Presence, (%)[J]	30 (7.7)	14 (7.5)	16 (7.9)	0.999*
Myocardial Muscle Bridge Presence, (%)[J]	5 (1.3)	3 (1.6)	2 (1.0)	0.674*
Gensini Score[J]	0.0 [0.0 – 50.5]	0.0 [0.0 – 32.0]	0.0 [0.0 – 50.5]	**0.039****
Mild Atherosclerosis (0-20)	377 (97.2)	183 (98.4)	194 (96.0)	0.278*
Severe Atherosclerosis (>20)	11 (2.8)	3 (1.6)	8 (4.0)	
Gensini Score Risk Categories[J]				
Low Risk (Gensini Score 0-20)	377 (97.2)	183 (98.4)	194 (96.0)	**0.049***
Moderate Risk (Gensini Score 21-40)	5 (1.3)	3 (1.6)	2 (1.0)	
High Risk (Gensini Score 41 and above)	6 (1.5)	0 (0.0)	6 (3.0)	

[J], n (%); [§]Median [Min-Max]; *Pearson Chi-Square; Fisher's Exact, or Fisher-Freeman-Halton test; **Mann-Whitney U test.

Table 4. Factors Associated with the Presence or Absence of Tortuosity: Results of Univariate and Multiple Binary Logistic Regression Analysis

	Univariate Logistic Regression		Multivariate Logistic Regression	
	Crude OR [95% CI]	Crude P value	Adjusted OR [95% CI]	Adjusted P value
Age	1.05 [1.03 – 1.07]	**<0.001**	1.04 [1.01 – 1.06]	**0.001**
Gender: *Male vs. Female*	0.29 [0.19 – 0.44]	**<0.001**	0.30 [0.16 – 0.59]	**<0.001**
Smoking Status: *Yes vs. No*	0.57 [0.36 – 0.91]	**0.019**	1.43 [0.75 – 2.76]	0.279
Hypertension: *Yes vs. No*	1.82 [1.21 – 2.73]	**0.004**	1.20 [0.73 – 1.96]	0.466
Diabetes: *Yes vs. No*	1.74 [1.03 – 2.93]	**0.039**	1.25 [0.67 – 2.31]	0.483
High-Density Lipoprotein	1.04 [1.02 – 1.06]	**<0.001**	1.02 [0.99 – 1.04]	0.155
White Blood Cells	0.90 [0.82 – 0.98]	**0.017**	0.96 [0.84 – 1.10]	0.544
Hemoglobin	0.78 [0.68 – 0.88]	**<0.001**	1.04 [0.89 – 1.22]	0.636
Lymphocytes	0.72 [0.56 – 0.94]	**0.014**	0.75 [0.54 – 1.05]	0.092
Platelets	1.01 [1.01 – 1.01]	**0.039**	1.01 [1.00 – 1.01]	0.099
Monocytes	0.25 [0.09 – 0.71]	**0.009**	0.76 [0.19 – 3.11]	0.707
Diastolic Dysfunction: *Yes vs. No*	2.11 [1.29 – 3.45]	**0.003**	1.58 [0.92 – 2.71]	0.097
Gensini Score	1.06 [1.01 – 1.11]	**0.012**	1.05 [1.01 – 1.11]	**0.049**

CI, Confidence Interval; OR, Odds Ratio.

Discussion

Findings of this study showed that the association between CAT and CAD is a multivariate and heterogeneous phenomenon. In this study, older age, female gender, and hypertension were prominent as significant risk factors for the development of CAT. This multivariate and heterogeneous etiology may influence specific hematological and biochemical markers in individuals with and without CAT and may complicate the interpretation of abnormalities in cardiac function and overall cardiovascular system performance when focusing on a single cause. Table 2 shows significant statistical differences in biochemical and hematological values in individuals with and without CAT, although these values were within normal ranges. As these individuals may have distinct characteristics, they could provide unique insights into CAT and CAD. Indeed, studies by Yurdam et al.,[19] Mihai et al.,[20] and Zebic Mihic et al.[21] have demonstrated that non-occlusive CAD and CAT are more closely associated with older age and female gender in patients referred for CAG. Additionally, several recent studies have shown an association between CAT and hypertension.[19,22-24] Interestingly, there were fewer smokers in the CAT group, which may relate to the lower prevalence of CAD in this group or to the study's single-center, retrospective design. Our findings support that CAT is more prevalent among women and older adults. Many other studies have shown similar results, highlighting the need for further investigation into the hormonal and physiological mechanisms underlying sex- and age-related differences in arterial structure.[12,24-26]

As shown in Table 3, CAT was significantly associated with impaired cardiac function. In our study, diastolic dysfunction was observed in 23.5% of the total population, compared with 29.7% among patients with CAT. Our findings suggest that the etiopathogenesis of echocardiographic diastolic dysfunction may be influenced by factors such as CAT, hypertension, older age, female gender, and smoking. Elamragy et al.[27] highlighted that CAT is associated with changes in left ventricular geometry and diastolic dysfunction due to hypertension-induced concentric hypertrophy. This study emphasizes a process in which alterations in blood flow, wall stress, and growth hormone levels are linked to left ventricular hypertrophy and CAT formation, resulting in diastolic dysfunction. Furthermore, diastolic dysfunction in CCS has been identified as a marker of CAT by Yurdam et al.[19] The relationship between CAT and diastolic dysfunction was further supported using three-dimensional (3D) speckle echocardiography in a study by Dogdus et al.[28] Our research supports an association between CAT and diastolic dysfunction. However, the lack of a significant association between diastolic dysfunction and CAT in multivariate analyses indicates that this relationship should be further investigated in multicenter, large-scale prospective studies.

In our study, there was no significant difference in coronary slow flow, muscle bridging, or coronary ectasia in the CAT group. However, CAT was associated with lower Gensini scores (< 20). Our findings also indicated that higher CAT scores were associated with Gensini scores reflective of lower atherosclerosis severity. This result may be due to a lower atherosclerotic plaque burden in patients with CAT. Multiple clinical studies have reported a statistically significant negative correlation between the presence of severe CAT and obstructive CAD, suggesting a possible inverse pathophysiological relationship between CAT and severe CAD. This may support further investigation into the pathophysiological processes in coronary flow dynamics in patients with CAT that may contribute to a lower atherosclerotic plaque burden. This perspective was supported by Zegers et al.,[10] Groves et al.,[25] Dominguez-Rodriguez et al.,[26] Li et al.,[29] and Khosravani-Rudpishi et al.[5] According to previous studies, older age, female gender, hypertension, and smoking are significant predictors of increased CAT and its severity.[24,25,29] The results of our study also align with these findings. However, Esfahani et. al.[24] reported no association between diabetes mellitus and CAT or its severity in their study.

Study Limitations

The major limitation of our study is its retrospective design, making selection bias possible despite our best efforts to minimize it by including consecutive patients. Due to the retrospective nature of our study, the indications for coronary angiography were limited to those we could access in the available data. Moreover, because of restricted access to historical data, we were unable to identify exactly which patients were sent for CAG because of a poor response to treatment or because of severe ischemia as documented by myocardial perfusion scintigraphy. Additionally, while CAT could be better assessed using 3D imaging, our evaluations were based on 2D images due to the available data. Although observer-to-observer and inter-observer differences in interpretation are limitations of this study, only patients for whom there was unanimous agreement on the presence of CAT were included. Additionally, our large sample size provided robust data, which was helpful for analytic purposes. However, the single-center nature of our study limits the generalizability of our findings across different populations. Further prospective studies are needed to verify these results and enhance our understanding and management of this condition by providing more insights into how CAT interacts with cardiovascular risk factors.

Conclusion

In this study, older age, female gender, and hypertension were identified as significant risk factors for CAT formation. Furthermore, our study demonstrated a significant association between CAT and diastolic dysfunction, which is often linked to hypertension. The presence of CAT was associated with lower Gensini scores and a reduced atherosclerotic burden. The lower Gensini scores observed in patients with CAT may be due to a reduced atherosclerotic plaque burden in these individuals. We believe that further research on this relationship could advance coronary atherosclerosis research and lead to new therapeutic strategies. Prospective, multidimensional studies are needed to investigate the complex mechanisms associated with CAT, improve risk stratification, develop more effective treatment algorithms, and establish new approaches to manage this condition.

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