ÖZGÜN ARAŞTIRMA / ORIGINAL RESEARCH

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The Relationship Between Vitamin D Deficiency And CHA_2DS_2-VASc Score in Chronic Coronary Syndrome

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Öz

Kronik Koroner Sendrom Tanısı Alan Hastalarda D Vitamini Eksikliği ile CHA_2DS_2-VASc Skoru Arasındaki İlişki

Amaç: Kronik koroner sendrom (KKS) tanılı hasta grubunda D vitamini eksikliği ile CHA_2DS_2-VASc skoru arasındaki ilişkiyi tespit etmeyi amaçladık.
Gereç ve Yöntem: Çalışmaya KKS tanısı konmuş ve koroner anjiografi uygulanmış ve kritik koroner arter darlığı saptanan 147 hasta retrospektif olarak alındı. Hastaların CHA_2DS_2-VASc skorları hesaplandı. Laboratuvar bulguları, D vitamin düzeyleri ve ekokardiyografi parametreleri kaydedildi. CHA_2DS_2-VASc skoruna göre; <3 ise düşük-orta skor grubu, skor ≥3 ise yüksek skor grubu olarak sınıflandırıldı.
Bulgular: Ortalama yaş: 62.7±10.5 ve hastaların 80 (%54.4)' i kadın idi. Yüksek skor grubundaki hastalar daha yaşlı idi (63.6±10.7, p<0.001). Vücut kitle indeksi (VKİ) ve diyabetes mellitus (DM) sıklığı yüksek skor grubunda daha fazlayken (p=0.003 ve p<0.001, sırasıyla), D vitamin düzeyi ve Ejeksiyon fraksiyonu ise anlamlı olarak daha düşüktü (p<0.001 ve p=0.02, sırasıyla). Çok değişkenli lojistik regresyon analizi yapıldığında, VKİ (Olasılık Oranı=1.383; %95 Güvenlik Aralığı=1.155-1.657), ve D vitamin düzeyinin (Olasılık Oranı=0.852; %95 Güvenlik Aralığı 0.776-0.935), yüksek CHA_2DS_2-VASc skorunu öngörme de bağımsız belirteçler olduğu izlendi. ROC analizi yapıldığında D vitamin düzeyi 23.6 ng/ml "kesim değeri" olarak alındığında %61 duyarlılık ve %84 özgüllük ile yüksek CHA_2DS_2-VASc skorunu belirlediği bulundu.
Sonuç: Kronik koroner sendrom tansıyla koroner anjiyografi uygulanan hastalarda düşük D vitamini düzeyi ile yüksek CHA_2DS_2-VASc skoru arasında bağımsız bir ilişki olduğu tespit edildi.
Anahtar Kelimeler: Kronik Koroner Sendrom, D Vitamin, CHA_2DS_2-VASc Skoru

Abstract

The Relationship Between Vitamin D Deficiency And CHA_2DS_2-VASc Score in Chronic Coronary Syndrome

Objective: To assess the relationship between Vitamin D level and CHA_2DS_2-VASc score in patients with chronic coronary syndrome (CCS).
Methods:A total of 147 participants with CCS who underwent coronary angiography and had critical coronary artery stenosis were retrospectively enrolled in the study. Patients' CHA_2DS_2-VASc scores were measured. Laboratory parameters including vitamin D and echocardiographic findings were recorded. Participants were divided into two groups according to CHA_2DS_2-VASc score, CHA_2DS_2-VASc score <3 as low-moderate group and CHA_2DS_2-VASc score ≥3 as high group.
Results: Mean age was 62.7±10.5 and 80 (54.4%) were female. Age was older in the group with high CHA_2DS_2-VASc score (63.6±10.7 vs 56.6±6.3, p<0.001). Body mass index (BMI) and diabetes mellitus (DM) frequency were higher in the high score group (p=0.003 and p<0.001, respectively), whilst ejection fraction and vitamin D level were lower (p=0.02 and p<0.001, respectively). In multivariate logistic regression analysis with forward selection, BMI (OR: 1.383, 95% CI: 1.155-1.657, p<0.001) and Vitamin D level (OR: 0.852, 95% CI: 0.776-0.935, p=0.001) were independently associated with high CHA_2DS_2-VASc score. A cut-off value of 23.6 ng/ml for vitamin D level predicted high CHA_2DS_2-VASc score, with 61% sensitivity and 84% specificity [AUC:0.755 (0.678-0.822), %95 CI, p<0.001] in receiver operating characteristic (ROC) curve analysis.
Conclusion: In patients with CCS undergoing coronary angiography, it was determined an independent relationship between low vitamin D levels and high CHA_2DS_2-VASc score.
Keywords: Chronic Coronary Syndrome, Vitamin D, CHA_2DS_2-VASc Score

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INTRODUCTION

Coronary artery disease (CAD) and ischemic stroke are predicted to be the leading causes of morbidity and mortality in developing countries. The coexistence of CAD and atrial fibrillation (AF) is common and a complex situation in terms of managing thromboembolic events. $CHADS_2$ and CHA_2DS_2-VASc scores are well-known markers to evaluate the risk of cardiac thromboembolism and to guide antithrombotic therapy in patients with AF (1). While many risk classifications are utilized for acute coronary syndromes (ACS), there is no well-accepted and widely used scoring system for assessing the risk of major adverse cardiac events (MACE) in patients with a diagnosis of chronic coronary syndrome (CCS). Few studies have shown that $CHADS_2$ and CHA_2DS_2-VASc scores, which show the risk of stroke in AF, could also be used to predict the risk of stroke and mortality after coronary artery bypass graft surgery in patients diagnosed with CAD, regardless of the presence of AF (2,3).

It has long been known that vitamin D plays a very important role in the skeletal system. Vitamin D deficiency was defined as serum levels of 25-(OH) Vitamin D <20 ng/ml, and Vitamin D insufficiency was defined as a level of 20–29 ng/ml. Plasma levels of 25-(OH) Vitamin D > 30 ng/ml were defined as normal (4). In nowadays, there is a great deal of evidence that vitamin D deficiency increases the risk of cardiovascular system disorders, hypertension (HT), diabetes mellitus (DM), and obesity, apart from skeletal system diseases (5,6). In addition to its modulatory effect on endothelial function, cardiomyocyte, and endothelial proliferation, vitamin D also affects the regulation of the inflammatory process that plays a crucial role in the development of atherosclerosis (7). Along with its association with all the mentioned diseases, some studies have also revealed the relationship between vitamin D level and the development of AF (8). Besides, Vitamin D deficiency has been shown to have a negative prognostic effect on cardiovascular and all-cause mortality, and every 10 ng / ml decrease in vitamin D level further increases the cardiovascular risk (9). It might be speculated that Vitamin D deficiency may contribute to mortality due to stroke and myocardial infarction by increasing the susceptibility to atrial fibrillation and affecting the atherosclerotic process secondary to inflammation. In our study, it was aimed to investigate the association of vitamin D levels with CHA_2DS_2-VASc score, which indicates thromboembolic burden and cardiovascular mortality, in patients diagnosed with CCS.

MATERIALS AND METHODS

Study population and design

This retrospective cohort study consists of a total of 147 patients with CCS, in accordance with the European Society of Cardiology 2019 Guidelines on CCS (10), undergoing coronary angiography (CAG) and had critical coronary artery stenosis between September 2017 to December 2020 at a single center. CAG was performed for patients who had positive treadmill exercise tests or signs consistent with ischemia on ECG, myocardial perfusion scintigraphy, or computed tomography CAG (128-slice), and whose chest pain persisted against medical therapy. Angina classification was done according to the Canadian Cardiovascular Society. 95 patients had positive treadmill exercise test, 46 had positive myocardial perfusion scintigraphy, and 6 had significant CAD on computed tomography CAG. Those with at least one of the following characteristics were excluded from the study; a) acute coronary syndrome, b) detected or known AF, c) secondary or uncontrolled hypertension, d) severe valvular disease (insufficiency or stenosis), e) acute/chronic renal or hepatic disease (ALT-AST>3-fold, creatinine>2.5 mg/dL or GFR<40 ml/min), f) presence of acute/chronic infection or autoimmune disease, and g) history of total thyroidectomy, hyper-, and hypoparathyroidism, or using calcium and vitamin D supplements.

The clinical and demographic characteristics, echocardiographic assessment, angiographic findings, and laboratory data of the study population were extracted from the archived records system and then analyzed. HT was determined according to at least 2 office blood pressure measurements of ≥140/90 mmHg obtained from the records on the different days, or the status of taking medication for HT. DM was determined according to the presence of the fasting blood glucose level of ≥126 mg/dl or status of taking medication for this disease. Body mass index (BMI) was calculated (kg/m^2). Subjects whose vitamin D levels were measured for various reasons within the last month before CAG were included in the study. Serum vitamin D level was measured using a direct competitive chemiluminescent immunoassay (Elecsys; Roche Diagnostics, Mannheim, Germany). Vitamin D levels were recorded as ng/ml. Blood samples were taken from the patients before the CAG procedure.

CAG was performed via a femoral approach using the standard Judkins technique (Siemens Axiom Sensis XP Berlin, German). Coronary lesions were evaluated by two experienced cardiologists who were unaware of the study data. Patients with stenosis of more than 50% in the left main coronary artery and/or more than 70% in at least one of the major epicardial coronary vessels were included in the study.

Standard echocardiographic evaluation was performed using commercially available equipment (Vivid7, GE Vingmed Sound, Horten, Norway) with a 2.5–3.5 MHz transducer. Left ventricular ejection fraction (EF) measurement was calculated using the modified Simpson method in 2D imaging. Myocardial performance index (MPI) obtained by Doppler examination was calculated by dividing the sum of isovolumic contraction time and isovolumic relaxation time by ejection time,

as suggested by Tei et al. (11) Devereux formula was used to calculate left ventricular mass. Then, the left ventricular mass index (LVMI) was obtained by dividing the left ventricular mass by body surface area.

The CHA_2DS_2-VASc score was calculated for each patient. Components of this score; congestive heart failure or left ventricular ejection fraction<40% (1 point), hypertension (1 point), age≥75 years (2 points), diabetes mellitus (1 point), stroke history (2 points), vascular disease (coronary arterial disease, peripheral vascular disease, carotid stenosis, etc.) (1 point), age 65-74 (1 point) and female gender (1 point). The total score that can be obtained is in the range of 0-9 (12). Since those with critical coronary artery stenosis were included in the study, CHA_2DS_2-VASc score was at least 1 for each individual of the study population. Participants were divided into two groups according to their CHA_2DS_2-VASc scores. If the CHA_2DS_2-VASc score is <3, it was classified as a low-moderate score group, if score ≥3, it was classified as a high score group.

Statistical analysis

An analytical (Kolmogorov–Smirnov test) method and visual methods (histograms and probability plots) were used to test the normality of distribution. Categorical variables were expressed as numbers and percentages (%), while continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range- IQR_{1-3}). Fisher's exact test and The Chi-square test were utilized to compare categorical variables. The Student t-test and the Mann-Whitney U test were used to compare continuous variables as appropriate. Spearman correlation coefficient was used to detect the association of CHA_2DS_2-VASc score with some biochemical parameters. All of the significant parameters in the univariate analysis with p<0.1 were selected for the multivariable model. Stepwise multivariate logistic regression analysis with forward selection was used to identify the independent predictors of a high CHA_2DS_2-VASc score. The odds ratio (OR) and 95% confidence interval (CI) of each independent variable were calculated. Receiver operating characteristic (ROC) curve analysis was used to determine the cut-off value of Vitamin D level for predicting high CHA_2DS_2-VASc score with the Youden index (Youden index = Max ([sensitivity] + [specificity] − 1). A 2-tailed p-value of<0.05 was considered significant throughout the study. In all statistical analyses; SPSS 20.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) and MedCalc statistical software v19.5.6 (Ostend, Belgium) were utilized.

RESULTS

The mean age of 147 patients with a diagnosis of CCS was 62.7±10.5 years and 54.4% of the patients were women. When the demographic characteristics of both groups were compared, it was found that the high CHA_2DS_2-VASc score group has a more advanced age and female gender (p<0.001, for each). While BMI and DM frequency were found to be higher in the high CHA_2DS_2-VASc score group (p=0.003 and p<0.001, respectively) than in the low-moderate score group, the percentage of current smokers was found to be higher in the latter (p<0.03) (Table 1). In the laboratory findings, for the former group; The HbA1c level was found to be high, whereas the vitamin D level was significantly lower (p=0.004 and p<0.001, respectively).

When echocardiographic and electrocardiographic findings are evaluated; ejection fraction and e / a ratio were lower in the high score group (p=0.02 and p=0.04, respectively), whilst MPI and the presence of ST-segment change were higher (p=0.001 and p=0.009, respectively). In the high CHA_2DS_2-VASc score group, the current use of an angiotensin-converting enzyme (ACE) inhibitor before the CAG procedure was higher (p=0.003). It was found a weak but significant correlation between the vitamin D level and the CHA_2DS_2-VASc score (Table 2), and as CHA_2DS_2-VASc score increased the mean vitamin D level decreased (Chart 1). In stepwise logistic regression analysis with forward selection; BMI (OR:1.383, 95% CI:1.155-1.657, p<0.001) and Vitamin D level (OR:0.852, 95% CI:0.776-0.935, p=0.001) predicted high CHA_2DS_2-VASc score (Table 3). A cut-off value of 23.6 ng/ml for vitamin D level predicted high CHA_2DS_2-VASc score, with 61% sensitivity and 84% specificity [AUC:0.755 (0.678-0.822), %95 CI, p<0,001] in ROC curve analysis (Chart 2).

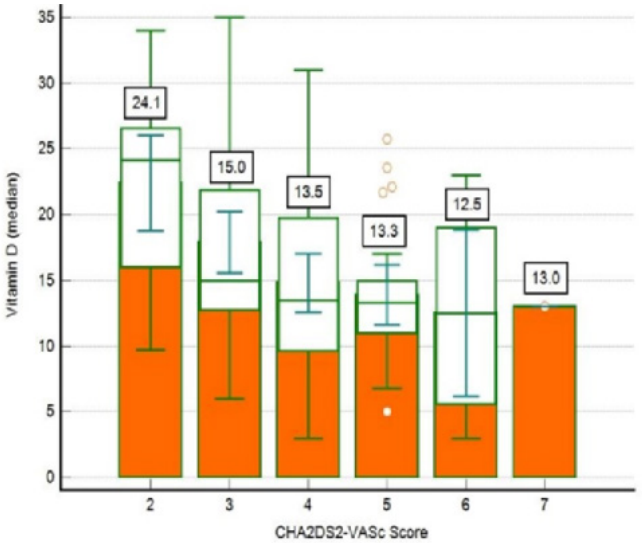

Chart 1. Median Vitamin D levels in CHA2DS2-VASc score

DISCUSSION

In the present study, it was evaluated the relationship between vitamin D deficiency and CHA_2DS_2-VASc score, which could be used to predict ischemic stroke and mortality, in patients with CCS and without AF. To the best of our knowledge, this is the first study to evaluate the association of Vitamin D level with CHA_2DS_2-VASc score. Consequently, it was found a

Table 1. Baseline characteristics of the study population

Variables	All (n:147)		Low Group (n:18)		High Group (n:129)		p value
Baseline characteristics	n	%	n	%	n	%	
Gender (female)	80	54.4	0	0	80	62	**<0.001**
Hypertension	43	29.3	2	11.1	41	31.8	0.071
Diabetes Mellitus	58	39.5	0	0	58	45	**<0.001**
History of family	78	53.1	12	66.7	66	51.2	0.217
Hyperlipidemia	60	40.8	5	27.8	55	42.6	0.230
Current smoker	43	29.3	9	50	34	26.4	**0.039**
Heart failure	27	18.4	1	5.6	26	20.2	0.197
Stroke/TIA	29	19.7	1	5.6	28	21.7	0.126
Vascular disease	53	36.1	3	12.2	50	38.8	0.067
Angina classification							0.549
CCS-1, n (%)	68	46.2	11	61.1	57	44.2	
CCS-2, n (%)	60	40.8	5	27.7	55	42.6	
CCS-3, n (%)	17	11.6	2	11.1	15	11.6	
CCS-4, n (%)	2	1.4	0	0	2	1.6	
Age, years	62.7±10.5		56.6±6.3		63.6±10.7		**<0.001**
BMI, kg/m^2	29.5±4.6		26.4±3.6		29.9±4.6		**0.003**
Laboratory Findings							
Fasting glucose, mg/dL	94.2±13.5		91.8±14.2		94.5±13.4		0.428
Creatinine, mg/dL	0.78±0.19		0.84±0.18		0.76±0.19		0.110
Uric Acid, mg/dL	5.0±1.5		5.4±1.3		4.9±1.5		0.263
GFR, ml/min/1.73 m^2	101.6±27.8		107.5±29.1		100.8±27.7		0.340
WBC, x10^3/µL	7.7±0.2		8.3±2.2		7.6±1.9		0.155
LDL, mg/dL	123.3±34.9		120.1±31.3		123.8±35.6		0.677
HDL, mg/dL	42.4±10.9		40.6±12.2		42.7±10.7		0.452
Total cholesterol, mg/dL	194.1±41.7		192.1±39.2		194.4±42.1		0.822
Triglycerides, mg/dL	157.6 (107.2-205.0)		145.5 (133.0-183.0)		163.0 (102.5-205.5)		0.991
CRP, mg/L	0.4 (0.2-0.8)		0.4 (0.2-0.7)		0.4 (0.2-1.1)		0.929
HgbA1$_c$, %	5.7 (4.9-7.3)		4.9 (4.4-5.8)		5.8 (5.1-7.4)		**0.004**
Heart rate, bpm	77 (70-83)		76 (67-79)		77 (70-83)		0.269
Vitamin D, ng/ml	14.4 (11.0-22.1)		24.2 (15.6-26.9)		14.0 (10.9-21.0)		**<0.001**
Echocardiographic Findings							
LVEF (%)	58.7±4.4		60.9±3.7		58.4±4.4		**0.021**
LVESD, mm	3.0±0.5		3.0±0.4		3.1±0.5		0.354
LVEDD, mm	4.5±0.6		4.4±0.5		4.5±0.6		0.618
LAD, mm	3.6±0.3		3.6±0.2		3.6±0.3		0.749
LVMI, gr/m^2	113.8±46.1		94.4±33.8		116.5±47.0		0.056
MPI	0.6 (0.4-0.7)		0.4 (0.4-0.5)		0.6 (0.4-0.7)		**0.001**
MV e/a ratio	0.9±0.3		1.1±0.3		0.9±0.3		**0.043**

Electrocardiographic features	n	%	n	%	n	%	
LVH	18	12.3	1	5.6	17	13.3	0.700
ST-segment change	48	32.7	1	5.6	47	36.4	**0.009**
T-wave negativity	29	19.7	2	11.1	27	20.9	0.528
Patholojical Q-wave	2	1.4	1	5.6	1	0.8	0.231
Medications before procedure	n	%	n	%	n	%	
ACE inh.	55	37.4	1	5.6	54	41.9	**0.003**
ARB	14	9.5	1	5.6	13	10.1	1.000
B-blockers	54	36.7	5	27.8	49	38	0.400
Asetil salicylic acid	64	43.5	6	33.3	58	45	0.351
Nitrat	7	4.8	2	11.1	5	3.9	0.207
Statin	27	18.5	2	11.1	25	19.5	0.310
Calcium channel blockers	9	6.2	0	0	9	7	0.295
Trimetazidine	6	4.1	0	0	6	4.7	0.447

ACE: Angiotensin-converting enzyme, **ARB:** Angiotensin II Receptor Blockers, **BMI:** body mass index, **CCS:** Canadian Cardiovascular Society, **CRP**: C-reaktif protein, **GFR:** Glomerular filtration rate, **HDL:** High density lipoprotein, **LDL**: Low density lipoprotein, **LAD:** Left atrium diameter, **LVEF:** Left ventricular ejection fraction, **LVEDD:** Left ventricular end diastolic diameter, **LVESD:** Left ventricular end systolic diameter, **LVH:** Left ventricular hypertrophy, **LVMI:** Left ventricular mass index, **MPI:** Myocardial Performance Index, **TIA:** Transient Ischemic Attack, **WBC:** White blood cell

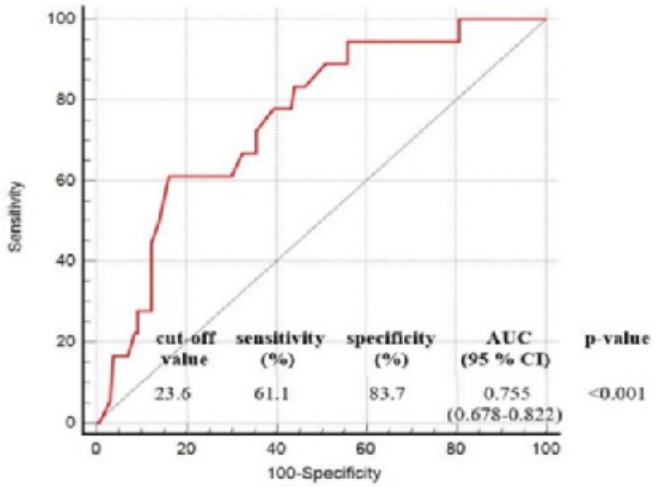

Chart 2. Receiver operating characteristic (ROC) curve of Vitamin D levels for the prediction of high CHA2DS2-VASc score

significant and inverse relationship between vitamin D deficiency and a high CHA_2DS_2-VASc score.

Although $CHADS_2$, CHA_2DS_2-VASc, and other similar scores are helpful in the risk stratification and treatment of patients with atrial fibrillation, most strokes (85%) occur in people with previously unknown AF (13). Patients diagnosed with CAD have an increased risk of stroke. In large patient cohorts of CAD, an independent association between each component of the $CHADS_2$ score and stroke has been demonstrated (14). In both $CHADS_2$ and CHA_2DS_2-VASc scores; 0 indicates low risk, 1 moderate risk, ≥ 2 high stroke risk. Welles et al. (3) revealed the relationship between the $CHADS_2$ score and stroke in stable CAD without AF. However, CHA_2DS_2-VASc score contains a broader group of patients such as vascular disease, patients aged 65-75 years, and female gender. Therefore, it might be expressed that $CHADS_2$ score is highly limited since each factor mentioned above contains 1 point and constitutes a medium risk on its own (15).

In a meta-analysis by Zhou et al. (16), $CHADS_2$ score was significant in predicting mortality in patients with CAD, irrespective of AF, while the risk of death was higher in patients without AF. Stroke risk was 2-fold higher in the high score group without AF diagnosis, but this relationship was not valid for patients with AF. The increased risk of both stroke and mortality in those without AF compared to those with AF has been attributed to the fact that the components of the score such as DM and heart failure may lead to left atrial remodeling and stasis and thereby embolism, independent of AF. Another explanation is that diseases such as DM and HT could directly accelerate the atherosclerotic process and endothelial dysfunction and may play a role in the etiology of stroke. In addition, it may be thought that the use of anticoagulants or antiaggregants in patients with AF may reduce thromboembolic complications (16). The $CHADS_2$ and CHA_2DS_2-VASc scores have also been shown in predicting major adverse cardiovascular events such as stroke, stent thrombosis, contrast-related nephropathy, no-reflow phenomenon, and severity of CAD (17-20). In another study, the well-known and widely accepted GRACE and TIMI risk scores were compared with $CHADS_2$ score in ACS patients, and $CHADS_2$ score was shown to be superior to the TIMI score, but no significant difference was observed between GRACE score and $CHADS_2$ score (21).

Vitamin D deficiency has been proven to contribute to the development of various chronic diseases such as HT, DM, CAD, stroke, and atherosclerosis (6). In a study by Verdoia et

Table 2. Association of CHA2DS2-VASc score with some biochemical parameters

	r*	p
LVEF, %	-0.142	0.087
LVMI, gr/m²	0.253	0.002
MPI	0.251	0.002
Vitamin D, ng/ml	-0.333	< 0.001
Body mass index, kg/m²	0.186	0.024

LVEF: Left ventricular ejection fraction, LVMI: Left ventricular mass index, MPI: Myocardial Performance Index *Spearman correlation coefficient

al. (22), patients with CAD undergoing percutaneous coronary intervention were included and was demonstrated that low vitamin D was associated with all-cause death and MACE including myocardial infarction and target vessel revascularization. In the NHANES III study; It was found that the development of angina, myocardial infarction, and heart failure was significantly higher in patients with low vitamin D levels (23). Previous studies have also revealed the association of vitamin D with the SYNTAX score, which shows the severity and prevalence of CAD (24). In addition, two meta-analyses have shown that low vitamin D is a possible risk factor for stroke (25). When all the mentioned studies are evaluated together, the role of vitamin D deficiency in the etiology of cardiovascular and cerebrovascular diseases and its relationship with CAD-related mortality and MACE has been presented. It was also found that vitamin D deficiency is associated with a high CHA_2DS_2-VASc score. The importance of this correlation might be explained by its contribution to the understanding that the vitamin D level may also be a risk factor for stroke. Besides, it is also useful to remind the association of vitamin D deficiency with certain disorders such as DM, HT, CAD, heart failure, and previous stroke, which are among the parameters of CHA_2DS_2-VASc score. An analysis by Liu et al. (26), which included 13 observational studies, has reported the relationship between vitamin D deficiency and increased risk of AF. Based on this study, it was speculated that the increased risk of stroke in patients with CAD might be primarily due to vitamin D deficiency or secondary to the development of AF. Although the importance of vitamin D deficiency in predicting cardiovascular risk is evident, the benefit of vitamin D supplementation in primary prevention from CAD and AF has not yet been proven (27-29). This lack suggests that vitamin D may be useful in diagnosis and risk classification rather than treatment, as predicted in our study.

Obesity is a well-known risk factor that increases susceptibility to diseases such as HT, DM, and CAD. Obese patients have structural changes in the heart, including increased left atrium diameter and left ventricular mass due to increased plasma volume, ventricular remodeling, and diastolic dysfunction (30). Therefore, both the frequency of AF and the tendency of AF to be permanent increase in such patients (31). Although Wan et al. (32) did not observe a significant relationship between BMI and $CHADS_2$ score in patients with non-valvular AF, they found that the risk of all-cause death and stroke was significantly higher in the high $CHADS_2$ score group. Survival rates were higher in the high CHADS2 score group for patients with BMI ≥24, while all-cause death was found to be higher in the intermediate $CHADS_2$ score group for patients with BMI<18.5 (32). The researchers attributed this result to the obesity paradox. The relationship of obesity with many cardiovascular diseases is explicit, but the obesity paradox remains unclear. Several potential explanations for this paradox are suggested. For instance, it has been claimed that the studies carried out had statistical errors, and the follow-up time and physical activity levels of the patients could have an effect on this paradox (33). Also, similar to the results of our study, Aksoy et al. showed that BMI is associated with CHA_2DS_2-VASc score (34). In addition, Wan et al. (32) studied a population with AF, whereas our study was conducted in non-AF patients with a higher risk of CAD. Another difference is that only Chinese patients were included in this study, so the consequences of many etiological factors such as genetics and eating habits underlying obesity due to racial and ethnic origin were ignored. As a result, most of the chronic diseases within CHA_2DS_2-VASc score are correlated with obesity. Therefore, the association of increased BMI with high scores is not surprising.

Table 3. Independent Predictors of High CHA2DS2-VASc score

Variable	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p	OR	95% CI	p
LVEF, %	0.845	0.736-0.970	0.017	-		-
Body mass index, kg/m²	1.227	1.069-1.409	0.004	1.383	1.155-1.657	<0.001
LVMI, gr/m²	1.014	1.000-1.028	0.056	-		-
Current smoker	0.358	0.131-0.976	0.045	-		-
Vitamin D, ng/ml	0.899	0.843-0.959	0.001	0.852	0.776-0.935	0.001
Diuretic use	2.967	0.817-3.231	0.322	-		-
ACE inh. use	12.240	1.581-94.784	0.016	-		-
ST-segment change	9.744	1.256-75.570	0.029	-		-

p-value <0.05 was considered significant. Nagelkerke R^2: 0.480, *p< 0.001*
ACE: Angiotensin-converting enzyme, **LVEF:** Left ventricular ejection fraction, **LVMI:** Left ventricular mass index

Limitations of the study

The present study has several limitations. Small sample size and cross-sectional design at a single center could be accepted as the main limitation. Second, the inclusion of only CCS patients as a CAD subset is a hurdle for the generalizability of the results. Third, Failure to take blood from the participants at a standard time and the diurnal rhythm of vitamin

D may have weakened the reliability of the study. Fourth, the low median vitamin D level, at the level of deficiency, of the study population could be considered both a strength and a limitation. This finding is a strong side because higher CHA_2DS_2-VASc score group is the dominant population of the study, so the result is consistent in this sense. On the other hand, this may be a limitation because the sample does not reflect the general population regarding vitamin D levels.

It was found that Vitamin D level was independently associated with a high CHA_2DS_2-VASc score in patients with CCS who underwent CAG and had critical coronary stenosis. This relationship of vitamin D, which is associated with many cardiovascular diseases including HT, atherosclerosis, DM, and CAD, with CHA_2DS_2-VASc score used in risk assessment for ischemic stroke, is very crucial in terms of providing us an alternative clinical approach for determining thromboembolism burden. Large-scale prospective randomized studies, however, are needed to better reveal this relationship and to elucidate its underlying physiopathological basis.

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Peer-Review

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

Permission was obtained from Malatya Clinical Research Ethics Committee for this study with date 22.01.2021 and protocol number 2021/27, and Helsinki Declaration rules were followed to conduct this study.

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