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Comparative Prognostic Value of CHA_2DS_2-VASc Score and Atherogenic Plasma Index for One-year Mortality Prediction in Ischemic Stroke Patients

CHA_2DS_2-VASc Skoru ve Aterojenik Plazma İndeksinin İskemik İnme Hastalarında Bir Yıllık Mortalite Tahminindeki Prognostik Değerlerinin Karşılaştırılması

Doğaç Okşen[1], Muzaffer Aslan[2], Yunus Emre Yavuz[2]

[1]Altınbaş University Faculty of Medicine, Department of Cardiology, İstanbul, Turkey
[2]Siirt University Faculty of Medicine, Department of Cardiology, Siirt, Turkey

Abstract

Objective: The CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, vascular disease, age, female gender) score is significantly associated with poor outcomes after ischemic stroke. However, the impact of lipid parameters on prognosis remains unclear. This study aimed to investigate the association between lipid parameters and outcomes, and compare them to the CHA_2DS_2-VASc score.

Method: A total of 583 ischemic stroke patients admitted between 2018 and 2022 were retrospectively analyzed. Demographic data, CHA_2DS_2-VASc scores, and lipid parameters, including ratio of triglyceride to high density lipoprotein (HDL-C), light density lipoprotein (LDL-C) to HDL and atherogenic plasma index (API) were recorded. Patients were followed for one year, with all-cause mortality as the primary endpoint. Predictors of mortality were determined using Cox regression analysis.

Results: The mean age of the 583 patients was 71.05±11.83 years, with a one-year all-cause mortality rate of 17.3% (n=101). Total cholesterol, non-HDL-C, and API were significantly higher in patients with poor outcomes (p=0.003, p=0.031, p=0.019, respectively). Both API and CHA_2DS_2-VASc scores were strong mortality predictors [hazard ratio (HR): 1.062, 95% confidence interval (CI): 0.973-1.252, p=0.007] and (HR: 1.567, 95% CI: 1.003-2.174, p=0.004), respectively. Receiver operating curve analysis revealed higher predictive power for CHA_2DS_2-VASc score compared to API (area under the curve: 0.756; p=0.014 vs. 0.568; p=0.045).

Öz

Amaç: CHA_2DS_2-VASc (konjestif kalp yetmezliği, hipertansiyon, ≥75 yaş, diabetes mellitus, inme, vasküler hastalık, 65-74 yaş, kadın cinsiyet) skoru, iskemik inme sonrası kötü sonlanımlarla önemli ölçüde ilişkilidir. Bununla birlikte, lipid parametrelerinin prognoz üzerindeki etkisi net değildir. Bu çalışma, lipid parametrelerinin sonlanımlar üzerindeki ilişkisini araştırmayı ve bunları CHA_2DS_2-VASc skoru ile karşılaştırmayı amaçlamıştır.

Yöntem: 2018 ve 2022 yılları arasında başvuran toplam 583 iskemik inme hastası retrospektif olarak analiz edildi. Hastaların demografik verileri, CHA_2DS_2-VASc skorları ve trigliserid/yüksek yoğunluklu lipoprotein (HDL-C) oranı, düşük yoğunluklu lipoprotein (LDL-C)/HDL-C oranı ve aterojenik plazma indeksi (API) gibi lipid parametreleri kaydedildi. Hastalar bir yıl boyunca takip edildi ve tüm nedenlere bağlı ölüm birincil sonlanım noktaları olarak kabul edildi. Mortalitenin öngördürücüleri Cox regresyon analizi ile belirlendi.

Bulgular: Beş yüz seksen üç hastanın ortalama yaşı 71,05±11,83 olup, bir yıllık tüm nedenlere bağlı mortalite oranı %17,3 (n=101) olarak saptandı. Toplam kolesterol, non-HDL-C ve API, kötü sonlanımları olan hastalarda anlamlı derecede daha yüksek bulundu (p=0,003, p=0,031, p=0,019, sırasıyla). Hem API hem de CHA_2DS_2-VASc skoru, güçlü mortalite öngördürücüleri olarak kabul edildi [tehlike oranı (HR): 1,062, %95 güven aralığı (GA): 0,973-1,252, p=0,007] ve (HR: 1.567, %95 GA: 1,003-2,174, p=0,004). Alıcı çalışma eğri analizinde, CHA_2DS_2-VASc skoru API'ya kıyasla daha yüksek öngörü olarak izlendi (eğri altındaki alan: 0,756; p=0,014 vs. 0,568; p=0,045).

Address for Correspondence: Doğaç Okşen, Altınbaş University Faculty of Medicine, Department of Cardiology, İstanbul, Turkey
E-mail: dogacoksen@gmail.com **ORCID:** orcid.org/0000-0003-4548-9543
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Conclusion: CHA_2DS_2-VASc and API are valuable predictors of one-year mortality after ischemic stroke. CHA_2DS_2-VASc score, which includes embolism risk factors, has stronger sensitivity and specificity for predicting poor outcomes compared to lipid parameters.

Keywords: Atherogenic plasma index, cholesterol, ischemic stroke, lipoprotein

Sonuç: CHA_2DS_2-VASc ve API, iskemik inme sonrası bir yıllık mortaliteyi öngörmede değerli prediktörlerdir. Tromboembolizm risk faktörlerini içeren CHA_2DS_2-VASc skoru, kötü sonlanımlar açısından lipid parametrelerine kıyasla daha güçlü duyarlılık ve özgünlüğe sahiptir.

Anahtar kelimeler: Aterojenik plasma indeksi, iskemik inme, kolesterol, lipoprotein

Introduction

Stroke is the third most common cause of death worldwide after cancer and coronary artery disease. Ischemic stroke is one of the most common forms of stroke and constitutes approximately 87% of all cases (1). Even if an individual survives a stroke, the risks continue; the incidence of death or recurrent stroke within 5 years is between 25% and 30% (2). Despite current treatment and a wide hospital network that allows rapid intervention, stroke outcomes are still not satisfactory.

The primary pathophysiology of the ischemic stroke involves atherosclerosis. Hyperlipidemia is one of the major contributing risk factors (3). Intimal thickening caused by the accumulation of low-density lipoprotein cholesterol (LDL-C) particles within the endothelium is the first step of atherosclerosis (4). Numerous studies have been conducted on the effects of various cholesterol markers on ischemic stroke and their role in its treatment (5). However, there is no sufficient consensus on the effects of cholesterol present during stroke on outcomes. Various cholesterol parameters, including total cholesterol (T-Chol), LDL-C, triglyceride (Tg), high density lipoprotein (HDL-C), non-HDL-C, Tg/HDL-C and atherogenic plasma index (API), have been studied to predict stroke outcomes (6,7).

CHA_2DS_2-VASc is a scoring system that includes the variables of congestive heart failure, hypertension, age ≥75, diabetes, previous stroke, vascular disease, age 65 to 74, and sex category (female). It has been used in cardiology guidelines for a long time to predict the risk of cardio-embolism in atrial fibrillation (AF) (8).

CHA_2DS_2-VASc score was found to be statistically significant in predicting 1-year major cardiovascular events in acute myocardial infarction (9). CHA_2DS_2-VASc score predicted all cause of mortality for both in hospital and medium term (one year) in patients underwent primary percutaneous coronary intervention due to ST-elevation myocardial infarction (10).

The CHA_2DS_2-VASc score is feasible in predicting stroke, but there are not enough clinical studies to support its use as a risk predictor independent of AF in ischemic stroke. AF is a risk factor that negatively affects one-year outcomes in ischemic stroke; however, isolated effects of the CHA_2DS_2-VASc score on prognosis in ischemic stroke are not clear (11). Scoring systems can provide important information about the patient's prognosis and current risks without creating additional costs for clinicians. In scoring systems and prognosis assessments, different lipid parameters and their ratios are frequently monitored in cardiovascular risk studies. Although many cardiovascular risk factors are included in the CHA_2DS_2-VASc score, there is no marker that directly shows lipid metabolism. For this reason, in our study lipid parameters were compared with the CHA_2DS_2-VASc score, despite the lack of a direct relationship between them. The aim of the study was to compare the effects of initial CHA_2DS_2-VASc and lipid parameters on one-year outcomes in patients with ischemic stroke.

Materials and Methods

Study Design and Population

This study was designed retrospectively and the raw data were obtained from the health care recording system between January 2018 and December 2022. Patients who were admitted to hospital with ischemic stroke were enrolled in this study. According to a medical database, 878 patients were hospitalized due to cerebrovascular events and 610 of those patients were hospitalized due to ischemic stroke. Twenty-seven patients were excluded due to hemorrhagic transformation during follow-up, missing data, and refusal to participate in the study. The absence of medical records or patients' permission, patients under eighteen years old, severe kidney, liver or congestive heart failure, simultaneous myocardial infarction or pulmonary embolism, end stage cancer, previous carotid artery intervention, were exclusion criteria. Patients who could not undergo magnetic resonance imaging (MRI) due to pacemakers or various body implants were not included in the study.

Every individual participant signed informed consent in accordance with regulations. The study protocol was approved by the Siir University's Ethics Committee

(no: 2022/12/01/02, date: 13.12.2022). The study was conducted in line with the ethical considerations set forth in the Declaration of Helsinki and Good Clinical Practice Guidelines. All participants included in this study were contacted by phone. Information about the individuals' conditions was obtained from them or their relatives. Data on those included in the study were obtained from the Ministry of Health's "e-pulse" system and hospital database.

Management of Stroke Patient

All patients presenting to the emergency department with a diagnosis of acute cerebrovascular accident were evaluated in accordance with the specific International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic algorithm (12). All patients underwent cranial computed tomography and MRI scans under the direction of neurology consultants. Cranial intracerebral and subarachnoid hemorrhages were excluded with neuroimaging. Neurological dysfunctions with symptoms lasting less than 24 hours were evaluated as transient ischemic attacks. Stroke severity was determined by neurology consultants according to the national institute of health stroke scale (NIHSS). Intravascular fibrinolysis and/or anti-platelet anti-coagulant treatment was decided in line with acute stroke guidelines. Patients with NIHSS score 6 and above and internal carotid artery or middle cerebral artery segment 1 occlusion were directed to mechanical thrombectomy if there were no contraindications. Fibrinolytic treatment was applied to patients younger than 80 years of age who presented within the first 3 hours of symptom onset, with NIHSS >25, with no previous stroke history, and not using oral anti-coagulants (13).

Data collection and clinical outcomes

Patient follow-up continued until death from any cause occurring after hospital admission. Demographic information, hemogram, lipid parameters, and other routine laboratory findings were obtained from the hospital database and recorded. Hemogram parameters, markers related to lipid metabolism, and their ratios were calculated and compared between groups. To prevent the possibility of bias, individuals with more than 20% missing data were not included in the study. All-cause mortality during the one-year follow-up period was accepted as the primary outcome. Subgroups of all-cause mortality were not specifically identified.

Statistical Analysis

All the statistical analysis was performed using SPSS version 23.0 (IBM SPSS Statistics, USA). Mean ± standard deviation was used for continuous variables, and for categorical variables, percentage and numbers were used. The distribution characteristics of variables were determined by Kolmogorov-Smirnov and Shapiro-Wilk tests. Non-normally distributed variables were presented as median, with minimum and maximum values. Normally distributed continuous variables were evaluated with paired samples t-test. Non-normally distributed variables were examined with the Mann-Whitney U test or the Kruskal-Wallis test. Categorical variables were compared with chi-square tests. Multi-variable Cox regression analysis was used to determine the independent predictors associated with primary outcomes. Cox proportional hazards models were used to calculate the hazard ratio (HR) and 95% confidence interval (CI) including variables of total-C, non-HDL cholesterol, API, Mon/HDL and CHA_2DS_2-VASc score. Receiver operating characteristic (ROC) curve analysis was applied to demonstrate the predictive power of variables for mortality in stroke follow-up. The area under the curve (AUC) was calculated with a 95% CI. Probability p-values of <0.05 were considered to indicate statistical significance.

Results

This study consisted of 583 patients who suffered from ischemic stroke. The mean age was 71.05±11.83 and 50.0% (n=292) of them were male. Mortality was defined during the one-year follow-up period among patients divided into two groups based on the primary end-point. The total mortality rates during one-year follow-up were 17.3% (n=101). The mean age was significantly higher in the mortality group (76.88±10.25 vs. 69.78±13.44; p=0.010). In the demographics of the population, hypertension, diabetes mellitus, atrial fibrillation, obesity, heart failure and atherosclerotic cardiovascular diseases had statistically higher prevalence in the non-survivor group (Table 1). T-Chol was significantly higher in mortality group (181.00±44.92 vs. 172.21±51.83, p=0.003). Tg and LDL-C were higher in the group with mortality, however, the difference is not statistically significant (p=0.511, 0.064, respectively). HDL-C was higher in the survival group, but not statistically significant (p=0.191). Non HDL-C and API were significantly higher in patients who had mortality in one year follow-up (138.58±42.51 vs. 131.34±49.04, p=0.031 and 0.52±0.25 vs. 0.48±0.27, p=0.019). Monocyte (MON) to HDL ratio was higher in survival group (0.013±0.19 vs. 0.03±0.39, p=0.047). The hemogram parameters were similar in each group except neutrophil which was higher in mortality group (7.14±4.35 vs. 6.10±3.25, p=0.006). The CHA2DS2-VASc score was found higher in patient who

had primary outcomes in one year rather than survival (5.16±1.49 vs. 4.94±1.68, p=0.005).

A multivariable logistic regression model was prepared with the variables of T-Chol, non-HDL-C, API, MON/HDL, and CHA2DS2-VASc score to determine the independent predictors increasing the mortality rate in the first year of stroke (Table 2). API and CHA_2DS_2-VASc were found to be independent variables to predict mortality during follow-up in the first year (HR: 1.062, 95% CI: 0.973-1.252, p=0.007; HR: 1.567, 95% CI: 1.003-2.174, p=0.004).

ROC analysis was used to compare the predictive power of API and CHA_2DS_2-VASc for predicting mortality during

Table 1. Initial demographics and laboratory findings of patients at admission and comparison according to 12-months follow-up

Variable	Mortality (n=101)	Survival (n=482)	p-value
Age, years	76.88±10.25	69.78±13.44	0.010
Male gender, % (n)	47.5 (48)	50.6 (244)	0.571
Hypertensiyon, % (n)	72.3 (73)	32.4 (156)	<0.001
Diabetes mellitus, % (n)	58.4 (59)	22.8 (110)	<0.001
Smoking habbits, % (n)	24.8 (25)	6.8 (33)	<0.001
Atrial fibrillation, % (n)	41.6 (42)	23.4 (113)	<0.001
Morbid obesity, % (n)	15.8 (16)	1.2 (6)	<0.001
Peripheral vascular disease, % (n)	15.8 (16)	3.9 (19)	<0.001
Heart failure, % (n)	32 (32)	9.5 (46)	<0.001
Coronary artery disese, % (n)	53.5 (54)	16.2 (78)	<0.001
Total-C, mmol/L	181.00±44.92	172.21±51.83	0.003
Triglyceride, mmol/L	194.14±75.26	188.79±69.64	0.511
HDL-C, mmol/L	40.87±11.20	42.41±10.70	0.191
LDL-C, mmol/L	113.70±37.71	106.01±38.93	0.064
Non-HDL-C, mmol/L	138.58±42.51	131.34±49.04	0.031
Tg/HDL-C	3.75±2.62	3.53±2.65	0.040
API	0.52±0.25	0.48±0.27	0.019
LDL/HDL	2.77±1.14	2.75±1.52	0.853
MON/HDL	0.013±0.19	0.03±0.39	0.047
WBC, cells/μL	9.77±4.28	9.08±3.78	0.105
Hemoglobin, g/dL	13.26±2.37	13.60±1.93	0.125
Platelet, cells/μL	235.92±87.97	249.63±76.79	0.112
RDW, cells/μL	52.39±10.51	50.24±10.65	0.065
Neutrophil, cells/μL	7.14±4.35	6.10±3.25	0.006
Lymphocyte, cells/μL	1.91±1.27	2.14±1.08	0.054
Monocyte, cells/μL	0.52±0.28	0.52±0.23	0.867
CHA_2DS_2-VASc, n	5.16±1.49	4.94±1.68	0.005

Total-C: Total cholesterol, HDL-C: High density lipoprotein, LDL-C: Light density lipoprotein, Tg: Triglyceride, MON: Monocyte, RDW: Red cell distribution width, WBC: White blood cell, API: Atherogenic plasma index

Table 2. Multivariable adjusted regression analysis for mortality in 12-months follow-up period

Variable	Exp (B)	Confidence interval	p-value
T-Chol	0.795	0.963-1.745	0.068
Non-HDL	1.051	0.996-1.125	0.084
API	1.062	0.973-1.252	0.007
MON/HDL	1.125	0.967-1.424	0.073
CHA_2DS_2-VASc	1.567	1.003-2.174	0.004

Total-C: Total cholesterol, HDL-C: High density lipoprotein, LDL-C: Light density lipoprotein, Tg: Triglyceride, MON: Monocyte

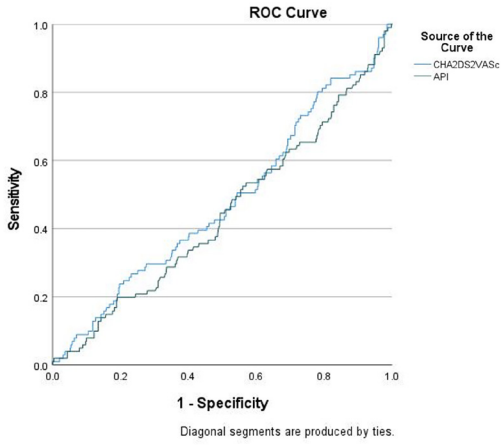

Figure 1. ROC analysis of CHA_2DS_2-VASc and API to compare their predictive ability for mortality after ischemic stroke

API: Atherogenic plasma index, ROC: Receiver operating characteristic

the first follow-up year (Figure 1). Accordingly, the API cut-off value of 0.48 predicted the development of with a sensitivity and specificity of 75.6% and 72.4%, respectively, (AUC: 0.568; 95% CI: 0.410-0.723; p=0.045). The CHA_2DS_2-VASc score was better than API to predict mortality (AUC: 0.756, 95% CI: 0.602-0.953; p=0.014). The sensitivity was 82.5%, and the specificity was 79%, with a cut-off value of 4.4.

Discussion

The average one-year mortality rate following ischemic stroke has been reported in the literature as 13-20% (14). In our study, the one-year all-cause mortality rate was observed to be 17.3%. This study aimed to predict one-year mortality after ischemic stroke using lipid parameters and the CHA_2DS_2-VASc score both API and CHA_2DS_2-VASc scores were identified as significant predictors of mortality. In the ROC analysis, API demonstrated a sensitivity of 75.6%, while the CHA_2DS_2-VASc score showed a higher sensitivity of 82.5%.

AF negatively affects outcomes in patients with ischemic stroke. Previous studies have reported that AF is an independent predictor of both mortality and cardiac embolism, particularly in cases involving large infarct territories (10). The CHA_2DS_2-VASc scoring system was developed to determine the risk of stroke in patients with AF. Recent studies have shown that a higher CHA_2DS_2-VASc score is associated with worse outcome after ischemic stroke. In a 3-month follow-up of 6,612 ischemic stroke patients, those with a CHA_2DS_2-VASc score of 2 or above experienced higher mortality and morbidity rates (15). In a 5-year follow-up study of 1,756 ischemic stroke patients without AF, intermediate and high-risk CHA_2DS_2-VASc scores were significantly associated with increased mortality risk compared to low-risk scores (HR: 3.56, 95% CI: 1.89-6.70) (16). Yang et al. (17) demonstrated that the CHA_2DS_2-VASc score lacks sufficient prognostic value after lacunar stroke in patients without AF. However, in patients with AF, a strong relationship between higher scores and poor outcomes was emphasized (17). In our study, the entire patient population was evaluated without distinguishing AF status, and the CHA_2DS_2-VASc score, was identified as a statistically significant predictor of one-year mortality in multivariate analyses (OR: 1.567, 95% CI: 1.003-2.174, p=0.004). The CHA_2DS_2-VASc scoring system serves as a valuable tool for clinicians in assessing thromboembolic risk and managing anticoagulation in cases of persistent or paroxysmal AF. Clinical studies have shown that the variables included in the CHA_2DS_2-VASc score are also useful for predicting patient prognosis. Its predictive power has been demonstrated in conditions such as heart failure and acute coronary syndromes, and recent studies have supported its feasibility in predicting post-stroke outcomes (18). In our study, the CHA_2DS_2-VASc score was significantly higher in the group with poor outcomes (p=0.005). It was also identified as a strong independent predictor of mortality within one year (HR: 1.567, p=0.004). These findings align with existing literature, supporting the use of the CHA_2DS_2-VASc score as a reliable variable for predicting poor outcomes in ischemic stroke follow-up.

Lipoproteins, Tg, and the API contribute to an increased frequency of athero-thromboembolic events in both coronary and cranial systems. However, their relationship with mortality after ischemic stroke remains unclear. While high LDL-C is linked to increased mortality in the general population, evidence in ischemic stroke patients is limited (19).

The widely accepted approach, “lower is better,” is contradicted by studies showing mixed results. In a 30-day follow-up of 45,669 ischemic stroke patients, those with T-Chol <120 mg/dL had a higher risk of mortality (HR: 1.29, p<0.001) (20). Among dialysis patients, both T-Chol <120 mg/dL and >200 mg/dL were associated with increased mortality (HR: 2.64 and 3.58, p<0.05) (20). High cholesterol contributes to inflammation and cytokine release; it increases thrombogenicity and reperfusion injury, making patients more vulnerable during recovery. A study by Tirschwell et al. (21) showed high T-Chol levels, increased

the mortality risk by 1.6 times, while another retrospective analysis reported a 2.17-fold increase in mortality with T-Chol >5.2 mmol/L (22).

TG, and TG derived metabolic indices were good predictors of cardiovascular events and demonstrated significant predictive ability during the follow-up period in terms of major adverse events. Liu et al. (7) compared different lipid metabolic markers as 3-month prognosis predictors in a prospective study including 1463 acute ischemic stroke patients. In the study, Tg (p=0.001), non-HDL-C (p=0.003), and API (p<0.001) were observed to be statistically significant and higher in groups with poor outcomes. HDL was found to be inversely correlated with outcomes (p=0.021) (7), suggesting that higher HDL levels were associated with less favorable outcomes.Our study is also in direct correlation with the literature in which T-Chol, non-HDL-C, Tg/HDL ratio and API were observed to be statistically significantly higher in the group with poor outcome. In the analysis in which mortality predictor variables were examined with Cox regression analysis, only API was statistically significant.

The CHA_2DS_2-VASc score is a widely applicable scoring system that offers valuable insights into the surveillance of diseases driven by athero-thromboembolic pathophysiology, impacting both the cardiac and vascular systems. Its ease of use and cost-effectiveness have contributed to its widespread adoption in clinical studies exploring patient outcomes. The variables included in the CHA_2DS_2-VASc scoring model are primarily established cardiovascular risk factors, with the exception of gender. While cardiovascular events are generally less frequent in women, their outcomes tend to be more severe and fatal, which explains this exception. Notably, the CHA_2DS_2-VASc score lacks any direct indicators related to cholesterol or its derivatives. However, cholesterol sub-derivatives, easily accessible and routinely measured, have been shown in the literature to provide valuable prognostic information. In our study, we evaluated the effects of the CHA_2DS_2-VASc score and cholesterol sub-derivatives on medium-term survival after ischemic stroke. While the API emerged as a strong predictor among cholesterol sub-groups, the CHA_2DS_2-VASc score proved to be an even stronger predictor of one-year mortality, likely due to its inclusion of a broader range of demographic and clinical variables.

Study Limitations

The main limitations of the study are that it was not designed prospectively, separate subgroups were not created for AF, and secondary outcomes such as recurrent stroke and hemorrhage were not included alongside the primary outcome points. The most significant limitation of the study is the lack of scoring systems that indicate the severity of stroke in patients. We believe that classifying patients based on stroke severity could have an impact on the results. The one-year follow-up is long enough to introduce bias into the study in terms of drug-patient compliance. In addition, the use of anticoagulant and/or antiplatelet agents was not specified in the study.

Conclusion

In ischemic stroke, both in-hospital and post-discharge mortality, as well as adverse events, affect more than one-fourth of the patients. It is important for clinicians to determine the patients' risks of adverse outcomes and to identify the factors that may lead to these risks. In patients with ischemic stroke, cholesterol levels detected at baseline were found to be higher in the group with poor outcomes. API was found to be a strong predictor that can be used in one-year follow-ups. CHA_2DS_2-VASc score is a stronger predictor than all cholesterol parameters in both determining the risk of thromboembolic events and predicting post-event prognosis. The CHA_2DS_2-VASc score is a more sensitive model in predicting mortality than the API.

Ethics

Ethics Committee Approval: The study protocol was approved by the Siir University's Ethics Committee (no: 2022/12/01/02, date: 13.12.2022). The study was conducted in line with the ethical considerations set forth in the Declaration of Helsinki and Good Clinical Practice Guidelines.

Informed Consent: Every individual participant signed informed consent in accordance with regulations.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.A., Y.E.Y., Concept: D.O., Design: D.O., Y.E.Y., Data Collection or Processing: M.A., Analysis or Interpretation: D.O., Y.E.Y., Literature Search: M.A., Writing: D.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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