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The Relationship Between HbA1c/C-Peptide Ratio and Ischemic Event in a Patient with Atrial Fibrillation: Retrospective Study

Atriyal Fibrilasyonu Olan Hastalarda HbA1c/C-Peptid Oranı ile İskemik Olaylar Arasındaki İlişki: Retrospektif Çalışma

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ABSTRACT Objective: Atrial fibrillation (AF) is a complex disease with irregular ventricular response and tachycardia as a result of irregular and rapid contraction of the atria. Many life-threatening ischemic events occur in AF. The aim of our study is to evaluate the HbA1c/C-peptide ratio (HCR) in AF patients with ischemic events. **Material and Methods:** The study was done retrospectively, and a total of 1,525 patients who were admitted to the cardiology outpatient clinic were recruited. The study's patient group with ischemic events consisted of 372 patients, and the group without ischemic events consisted of 853 patients. HCR was evaluated by dividing the patients into two groups. **Results:** It was observed that the HCR (3.41±1.18 vs 2.15±1.01, p<0.001) was statistically significantly higher in the group with an ischemic event compared to the group without an ischemic event. In the ROC analysis, the cut-off value of the HCR score in the group with an ischemic event was found to be 79% sensitivity and 81% specificity. It was determined as 2.82 (AUC=0.821, CI95=0.682-0.889, p<001). In multivariate logistic regression analysis, HCR were identified as potential independent predictors of experiencing an ischemic event. **Conclusion:** In our study, the HCR was found to be higher in patients who developed ischemic events, and in statistical analysis, it was found to be an independent determinant of ischemic events in AF patients. Our study is the first to evaluate this situation. Therefore, the HCR may be an important parameter that should be used in the follow-up of AF patients experiencing ischemic events.

Keywords: Atrial fibrillation; HbA1c; C-peptide; HbA1c/C-peptide ratio; ischemic event

ÖZET Amaç: Atriyal fibrilasyon (AF), atriyumların düzensiz ve hızlı kasılması sonucu düzensiz ventriküler yanıt ve taşikardi ile karakterize karmaşık bir hastalıktır. AF'de yaşamı tehdit eden birçok iskemik olay meydana gelir. Çalışmamızın amacı, iskemik olay yaşayan AF hastalarında HbA1c/C-peptid oranını (HCR) değerlendirmektir. **Gereç ve Yöntemler:** Çalışma retrospektif olarak yapılmış olup, kardiyoloji polikliniğine başvuran toplam 1.525 hasta çalışmaya dâhil edilmiştir. Çalışmanın iskemik olay yaşayan hasta grubu 372 hastadan, iskemik olay yaşamayan grup ise 853 hastadan oluşmuştur. HCR, hastalar iki gruba ayrılarak değerlendirilmiştir. **Bulgular:** İskemik olay yaşayan grupta HCR'nin (3,41±1,18'e karşı 2,15±1,01, p<0,001) iskemik olay yaşamayan gruba göre istatistiksel olarak anlamlı derecede daha yüksek olduğu gözlendi. ROC analizinde iskemik olay yaşayan grupta HCR skorunun kesme değeri 2,82 (AUC=0,821, CI95=0,682-0,889, p<0,001), ve %79 duyarlılık ve %81 özgüllük olarak saptandı. Çok değişkenli lojistik regresyon analizinde HCR, iskemik olay yaşamanın potansiyel bağımsız öngördürücüsü olarak tanımlandı. **Sonuç:** Çalışmamızda iskemik olay yaşayan hastalarda HCR'nin daha yüksek olduğu ve istatistiksel analizde AF hastalarında iskemik olayların bağımsız bir belirleyicisi olduğu bulundu. Çalışmamız bu durumu değerlendiren ilk çalışmadır. Bu nedenle, HCR iskemik olaylar yaşayan AF hastalarının takibinde kullanılması gereken önemli bir parametre olabilir.

Anahtar Kelimeler: Atriyal fibrilasyon; HbA1c; C-peptid; HbA1c/C-peptid oranı; iskemik olay

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Atrial fibrillation (AF) is the most common type of arrhythmia, occurring in approximately 2.3-3.4% of the population, and its prevalence is estimated to double by 2050.[1] AF poses a serious public health problem by increasing cardiovascular morbidity and mortality as well as the cost of healthcare services.[2] Glycated hemoglobin (HbA1c) is a healthy biochemical indicator of glucose control within 2-3 months and is frequently used in daily clinical practice. The relationship between HbA1c and AF has been investigated in previous studies, but the data are not clear.[3] A study conducted in Japan found that higher HbA1c reduced the risk of AF.[4] In another study conducted with atherosclerosis, it was shown that high HbA1c increased the risk of AF.[5]

Diabetes mellitus (DM) is a prothrombogenic disease, and although the actions underlying the increased susceptibility to thrombosis in Type 2 DM (T2DM) have not been fully elucidated, it is assumed that it is bioactive roles of HbA1c and C-peptide may play an important role.[6] However, it has been shown that these two markers can also affect important bioactive pathways in non-diabetic patients.[7] HbA1c is not only a diagnostic parameter of diabetes but also a predictive biomarker of cardiovascular problems for diabetics and non-diabetics.[8] HbA1c elevation has been shown to increase platelet activation and aggregation.[9] Additionally, close glycemic control, i.e. lowering HbA1c, has been shown to reduce platelet reactivity in patients with acute coronary events presenting with hyperglycemia.[10] C-peptide is a bioactive molecule that is transferred to the circulation equimolarly with insulin from beta cells in the pancreas by the degradation of proinsulin.[11] Beyond showing the pancreatic beta cell reserve, it has been shown to play an active role in many molecular pathways beyond the pancreatic beta cell reserve.[12] It has been shown that high doses of C-peptide can reduce thrombus formation.[13] C-peptide regulates the interactions of leukocytes, erythrocytes and platelets with the endothelium.[14] Therefore, C-peptide shows positive effects on homeostasis and inflammatory processes that play a role in triggering thrombosis, a complication of atherosclerosis.[15]

Considering all these results, the HbA1C/C peptide ratio (HCR) obtained by combining two biomarkers into a single fraction may better predict ischemic events in AF patients due to the prothrombogenic effect of HbA1c and the antithrombogenic effect of C-peptide. In this context, in this study, we wanted to demonstrate the accuracy of this assumption in AF patients.

MATERIAL AND METHODS

STUDY DESIGN STUDY POPULATION

This retrospective study was conducted with data from 1,525 AF patients at a local university hospital cardiology outpatient clinic between April 2020 and April 2024. Our study complies with the principles of the Declaration of Helsinki and was approved by the Tokat Gaziosmanpaşa University Faculty of Medicine (date: June 6, 2024, no: 83116987-378) of our local university hospital.

Patients were found from the local hospital database system and added to the study. A total of 300 patients were not included in the study due to lack of data. The study was completed with 1,225 patients. AF patient group; Patients who experienced an ischemic event (n=372) and patients who did not experience an ischemic event (n=853) were classified into two groups, and these classified groups were evaluated based on the HCR score. Documented 12-lead electrocardiography revealed AF (absence of distinct repetitive P waves, irregular atrial activity). A period of at least 30 seconds was determined to determine the diagnosis of AF.[2] Ischemic event; In patients with AF, an ischemic event occurring after thrombus formation in any organ or vascular structure was accepted. Acute infection or sepsis, central venous catheter, left ventricular apical thrombus, acute heart failure (HF), severe valve disease (moderate mitral stenosis and all other serious valve diseases and prosthetic valve disease), malignancy, coagulation disorders, under 18 years of age, storage diseases (glycogen, lipid, lysosomal, etc.), acute kidney disease, mechanical valve, end-stage renal disease, and severe anemia were not included in the study.

ECHOCARDIOGRAPHY AND ELECTROCARDIOGRAPHY EVALUATION

The patients were evaluated in the echocardiography (ECO) department of our center by two experienced

cardiologists in the left decubitus state using an EPIQ 7 ECO device (Philips, Amsterdam, Netherlands) and a 2.5-3.5 MHz transducer. The left ventricular ejection fraction of all patients was determined by the modified Simpsons method.

After the patients rested for at least thirty minutes, a 12-lead ECG (Cardiofax V; Nihon Kohden Corp., Tokyo, Japan; 10 mm/mV and 25 mm/sec) was taken by experienced technicians in the supine position under the supervision of a cardiologist.

LABORATORY, DEMOGRAPHIC DATA AND RISK SCORE

All patients were required to be non-smokers or fast for 8 hours before blood samples were taken. Biochemical parameters were evaluated with the Beckman Coulter LH-750 Hematology Analyzer (Beckman Coulter, Inc, Fullerton, California). Lipid panel data obtained by standard evaluation were taken. For the diagnosis of hypercholesterolemia, ligh densisity lipoproteine value was determined to be higher than 130 mg/dL and those who were previously diagnosed with hypercholesterolemia or were treated for hypercholesterolemia. DM was defined as fasting serum glucose value ≥126 mg/dL, HbA1c≥6.5%, or using DM medication. For the diagnosis of hypertension, intermittent systolic/diastolic blood pressure measurements were taken after thirty minutes of rest, and patients whose value was higher than 140/90 mmHg or who had previously received treatment with a diagnosis of hypertension were included. Patients who continued to smoke for the last six months were determined as smokers. In patients with rheumatic valve disease, mild mitral stenosis was accepted as mitral valve gradient <5 mmHg. According to the European Society of Cardiology guideline, patients with chronic coronary syndrome were considered to have coronary artery disease (CAD).[16] HCR; It was calculated by dividing HbA1c to C-peptide. CHA_2DS_2-VASc (C: congestive HF or left ventricular systolic dysfunction, H: hypertension, A: ≥75 years, D: DM, S: previous stroke, V: vascular disease, A: 65 to 74 years, and Sc: female gender) scores of all groups were calculated.

STATISTICS

The data of our study were examined with SPSS 25.0 (SPSS, Inc., Chicago, IL, USA). In statistical significance tests, $p \leq 0.05$ was taken. The Kolmogorov-Smirnov test was applied to evaluate the normality of the distribution of continuous variables. Continuous variables were expressed as mean±standard deviation or median (interquartile range), and comparison was made with student t or Mann-Whitney U tests, depending on distribution. Categorical variables were expressed as percentages and numbers and compared with the χ^2 test. The best cut-off values of HCR were calculated by (ROC) curve analysis. In grouping HCR values as high and low, the best cut-off value obtained from the ROC curve of HCR was accepted as the cut-off value. Variables that were significant ($p<0.05$) in the univariate Cox proportional regression analysis were included in the multivariate Cox proportional regression analysis. The results of the Cox regression analysis are reported as hazard ratio (HR) and 95% confidence interval (CI).

RESULTS

1,225 patients with AF included in the study. Basic demographic characteristics, clinical laboratory values, echocardiographic data and treatments used by the patients who experienced ischemic events included in the study are listed in Table 1. Age, diabetes, heart rate and CHA2DS2-VASc score were calculated to be higher in the group with AF diagnosed with ischemic events (Table 1). NT-pro BNP value was found to be higher in the group experiencing AF and ischemic events. HbA1c value was found to be significantly higher in patients who experienced ischemic events when compared to patients who experienced ischemic events and patients who did not experience ischemic events. C-peptide value was found to be higher in the group that did not experience ischemic events. The HCR score was found to be statistically significantly higher in patients who experienced an ischemic event than in patients who did not experience an ischemic event (Table 1). The events that occurred in patients who developed ischemic events were as follows; transischemic attack in 245 patients (65.86%), ischemic stroke in 100 patients (26.88%), mesenteric ischemia in 7 patients

TABLE 1: Comparison of patients' demographics, hematological, echocardiographic and medical treatments.

Variable	Ischemic event (n=372)	No ischemic event (n=853)	p value
Demographics features			
Age (years)	62±10.3	58.2±11.2	0.002
Female gender n (%)	189 (50.8)	435 (50.99)	0.289
BMI kg/m^2	29.23±4.23	28.43±3.3	0.473
CAD n (%)	119 (31.98)	257 (30.12)	0.243
Diabetes mellitus n (%)	167 (44.89)	341 (39.97)	0.007
Hypertension n (%)	156 (41.93)	358 (41.96)	0.537
Hyperlipidemia n (%)	85 (22.84)	196 (22.97)	0.943
Smoking n (%)	120 (32.25)	267 (31.30)	0.176
HF n (%)	81 (21.77)	180 (21.10)	0.195
Heart rate (bpm)	127.68 (55-139)	102.52 (53-141)	0.003
CHA_2DS_2-VASc score	4.57 (0-7)	3.18 (0-7)	<0.001
Laboratory findings			
Glucose (mg/dL)	127.23±11.43	125.18±12.21	0.437
Creatinin (mg/dL)	1.12±0.53	1.09±0.57	0.931
BUN (mg/dL)	25.4±11.2	26.3±11.01	0.352
Sodium (mmol/L)	137.62±12.09	139.01±9.34	0.723
Potassium (mmol/L)	3.55±1.31	3.78±0.85	0.837
Albumin (g/dL)	4.52±1.32	4.32±1.57	0.381
ALT (U/L)	28.44±1.45	29.38±1.51	0.349
AST (U/L)	22.63±4.17	23.57±3.68	0.553
TSH (µIU/mL)	1.88±0.87	1.93±0.99	0.738
T4 (µIU/mL)	1.23±0.57	1.30±0.77	0.182
Haemoglobin (g/dL)	10.21±2.26	11.20±1.38	0.340
WBC count (x10^3/µl)	11.96±1.27	11.23±1.53	0.473
Platelet (x10^3/µl)	358.66±21.56	366.11±23.59	0.188
LDL-cholesterol (mg/dL)	131.26±21.33	130.61±22.53	0.364
HDL-cholesterol(mg/dL)	32.64±4.77	31.62±5.73	0.281
Triglyceride, (mg/dL)	231.13±11.57	229.14±12.55	0.137
NT-pro BNP (pg/mL)	593.28±57.63	420.36±53.46	0.015
HbA1c	7.83±1.2	6.23±1.2	<0.001
C-peptide	2.23±0.8	3.76±0.78	<0.001
HCR	3.41±1.18	2.15±1.01	<0.001
Echocardiographic parameters			
LVEF (%)	50.12±5.34	51.43±5.47	0.453
LA size (mm)	48.52±9.53	43.28±8.52	0.032
LVDD (mm)	48.22±2.2	47.43±2.1	0.266
LVDS (mm)	34.61±2.8	35.44±2.78	0.519
IVSD (mm)	10.62±2.4	10.43±2.1	0.599
E/e'	13.83±2.7	13.79±3.1	0.239
Mild mitral stenosis n (%)	55 (14.78)	127 (14.88)	0.979
Medications			
Acetylsalicylic acid n (%)	18 (4.83)	41 (4.80)	0.539
ACE I, ARB n (%)	189 (50.80)	418 (49)	0.161
Beta bloker n (%)	297 (79.83)	682 (79.95)	0.637
Statin n (%)	186 (50)	435 (50.99)	0.527
Calcium channel blokers n (%)	111 (29.83)	255 (29.89)	0.681
Dihydropyridine	40 (10.75)	93 (10.90)	0.791
Nondihydropyridine	82 (22.04)	187 (21.92)	0.837
Anticoagulant medication n (%)	358 (96.23)	812 (95.19)	0.561
Warfarin	21 (5.64)	42 (4.92)	0.781
Apixaban	102 (27.41)	238 (27.90)	0.697
Rivaroxaban	115 (30.91)	264 (30.94)	0.738
Edoxaban	99 (26.61)	223 (26.14)	0.957
Dabigatran	21 (5.64)	45 (5.27)	0.473

BMI: Body mass index; CAD: Coronary artery disease; HF: Heart failure; WBC: White blood cells; BUN: Blood urea nitrogen; NT-proBNP: N-terminal brain natriuretic peptide; ALT: Alanin aminotransferase; AST: Aspartat aminotransferase; TSH: Thyroid-stimulating hormone; WBC: White blood cell; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; LVEF: Left Ventricular ejection fraction; LVDD: Left ventricular end diastolic diameter; LVSD: Left ventricular end systolic diameter; LVPWT: Left ventricular posterior wall thickness; IVSD: Interventricular septum; LA: Left atrium; HbA1c: Haemoglobin A1c; HCR: HbA1c/C-peptide ratio.

(1.88%) and chronic thromboembolic event in 20 patients (5.37%).

In the ROC analysis, the cut-off value of the HCR value in patients experiencing AF and ischemic events was found to be 2.82, with 79% sensitivity and 81% specificity (AUC=0.821, CI95=0.682–0.889, p<001) (Figure 1). In the ROC analysis, the cut-off value of the HbA1c value in patients experiencing AF and ischemic events was found to be 6.82, with 71% sensitivity and 70% specificity (AUC=0.712, CI95=0.542-0.763, p<001) (Figure 1). In the ROC analysis, the cut-off value of the C peptide value in patients experiencing AF and ischemic events was found to be 2.72, with 70% sensitivity and 68% specificity (AUC=0.692, CI95=0.512-0.753, p<001) (Figure 1). In multivariate logistic regression analysis, diabetes, CHA2DS2-VASc score, LA size, HCR were determined to be independent potential predictors of experiencing AF and experiencing an ischemic event (Table 2).

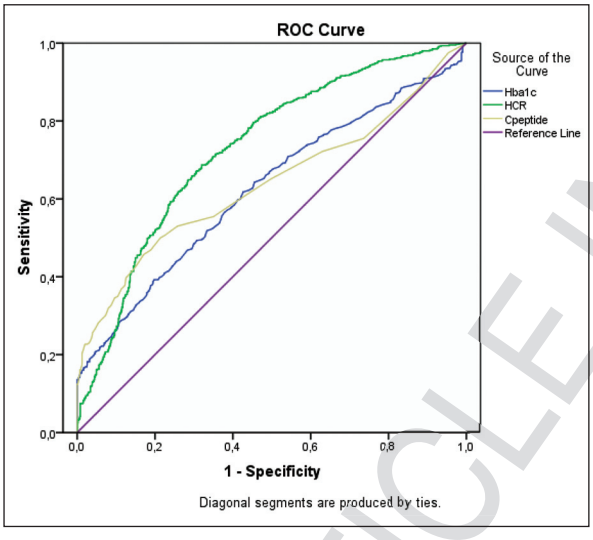

FIGURE 1: ROC curve analysis of HCR to predict ischemic events due to atrial fibrillation.
HCR: HbA1c/C-peptide ratio.

DISCUSSION

As a result of our study, we found that there is a significant relationship between ischemic events and HCR in AF patients. This study is the first to investigate the relationship between ischemic events and HCR in patients diagnosed with AF. A previous study found a significant positive relationship between HbA1c values and AF duration, indicating that impaired glucose metabolism is associated with increased AF burden.[17] Considering that DM increases the thromboembolic risk in AF and further exacerbates arrhythmia, HbA1c values may be a useful tool in strategies aimed at reducing the burden of AF and associated pathologies. Supporting this idea, a study showed that HbA1c is directly related to the risk of stroke and that HbA1c assessment increases the accuracy of predicting stroke in patients diagnosed with DM with AF.[18] Another publication showed that high HbA1c values may increase the risk of AF in patients diagnosed with DM.[19] Poor glycemic control demonstrated by increased HbA1c values is an independent risk factor for AF.[20] Various pathophysiological mechanisms have been put forward to explain this relationship. First, HbA1c, a protein with a long half-life, has been shown to be a reliable marker not only for the diagnosis of DM, but also for identifying peo-

TABLE 2: Univariate and multivariate regression analysis to identify independent predictors in patients with atrial fibrillation experiencing ischemic events.

	Univariate analysis		Multivariate analysis	
Variable	**Odds ratio (95% CI)**	**p value**	**Odds ratio (95% CI)**	**p value**
Age	1.254 (0.892-1.372)	0.002	0.852 (0.542-0.915)	0.679
Diabetes mellitus	**1.851 (1.032-1.984)**	**0.007**	**1.472 (1.120-1.823)**	**0.031**
Heart rate	1.185 (0.136-1.788)	0.003	0.941 (0.781-1.120)	0.329
CHA2DS2-VASc score	**1.286 (0.650-1.824)**	**<0.001**	**1.324 (1.012-1.565)**	**<0.001**
NT-pro BNP (pg/mL)	1.583 (1.012-1.812)	0.015	0.991 (0.831-1.103)	0.451
LA size (mm)	**1.273 (0.963-1.521)**	**0.032**	**1.251 (0.845-1.423)**	**0.030**
HCR	**3.124 (2.213-4.310)**	**<0.001**	**3.216 (2.334-4.365)**	**<0.001**

NT-proBNP: N-terminal brain natriuretic peptide; LA: Left atrium; HbA1c: Haemoglobin A1c; HCR: HbA1c/C-peptide ratio; CI: Confidence interval.

ple at high risk for cardiovascular pathologies, with or without DM.[21] High HbA1c values have been associated not only with long-term damage to glycolipid metabolism but also with low-grade systematic inflammation and progression of atherosclerotic diseases.[22] In a community study, high HbA1c values were associated with markers of systemic inflammation such as D-dimer, C-reactive protein, white blood cell count, uric acid and fibrinogen.[23] The relationship between oxidative stress and inflammation and AF formation attracts attention.[24] Additionally, excessive secretion of collagen proteins may increase atrial activation time and cycle length, and reduce atrial voltage, which creates a substrate for the development and maintenance of AF.[25] Therefore, high HbA1c values may be related to inflammatory events in the pathophysiology of AF.

DM is a prothrombotic disease that creates a hypercoagulable state.[6] It contributes to this condition mainly by increasing endothelial dysfunction and platelet activation and aggregation.[26] Although various mechanisms are involved in platelet hyperactivation and aggregation in these patients, highly glycosylated hemoglobin plays an important role in these patients.[10] HbA1c has also been shown to be an important prognostic marker in non-diabetics.[7] It has been suggested that HbA1c contributes to this interaction by inhibiting platelet activation and nitric oxide (NO) production; this prevents platelets from adhering to the vascular endothelial region by increasing the amount of cytoplasmic cyclic guanosine monophosphate present in platelets or mediated by peripheral β-adrenoceptors.[9] Lowering HbA1c has also been shown to negatively affect platelet hyperactivity in patients experiencing acute coronary syndrome with poor glycemic values.[10] C-peptide is a marker of the pancreatic reserve state, which is secreted from pancreatic beta cells in equimolar amounts with insulin upon the breakdown of proinsulin and plays a bioactive role in many molecular pathways.[12] Since its half-life is longer than insulin, it is a useful and frequently used marker used in clinics today to find the cause of hypoglycemia, regulate diabetes treatment, and evaluate the distinction between T1DM and T2DM when diagnosed. In contrast to HbA1c, C-peptide has been well documented in studies to provide antithrombotic properties by positively affecting microvascular blood flow and blood hemorheology through different mechanisms.[27] It has been determined that excessive amounts of C-peptide may reduce thrombus formation.[13] NO is a molecule that plays a special role in preventing the activation and aggregation of platelets, and studies have shown that it is involved in many bioactive effects of C-peptide.[28] It has been determined that C-peptide-induced NO formation may be beneficial in cardiovascular events by preventing the interaction of erythrocytes and leukocytes with the endothelium in vitro.[14] It has been shown to increase the amount of skin microvascular blood flow in DM patients by stimulating Na+, K+-ATPase activity and NO formation.[29] In contrast to HbA1c, C-peptide has been shown to improve erythrocyte deformation by increasing Na+, K+-ATPase activity.[30] In an in vitro study with immobilized endothelial cells, it was shown that C-peptide could inhibit the adhesion of platelets to the endothelium in the presence of erythrocytes.[31] In another study, C-peptide was shown to induce NO formation in both endothelium and platelets by stimulating the formation of adenosine triphosphate (ATP) in erythrocytes.[32] C-peptide has been found in many studies to reverse the consequences of NO depletion and deficiency in many tissues.[33] Endothelial dysfunction is associated with decreased NO production and increased reactive oxygen samples (ROS) production, leading to obstruction of blood flow and predisposition to atherogenesis and thrombosis in vessels.[34] C-peptide has been shown to inhibit endothelial apoptosis due to hyperglycemia and reduce NADPH oxidase-induced production of ROS in the human aorta.[35] Additionally, C-peptide has been found to reduce ROS production through AMPK (activated protein kinase) activation and vascular endothelial growth factor inhibition. In contrast to C-peptide, ROS production increases in chronic hyperglycemic states as determined by HbA1c.

In our study, HbA1c was higher and C-peptide value was lower in AF patients who experienced ischemic events. AF patients are prone to ischemic events, but high HbA1c and low c peptide further increase this situation. HCR rate is directly proportional to HbA1c value and inversely proportional to C-pep-

tide level. For this reason, the HCR rate was found to be higher in patients with ischemic events, and in statistical analysis, it was found to be an independent predictor of ischemic events in patients diagnosed with AF. Therefore, HCR rate is an important parameter that should be used in the diagnosis and follow-up of AF patients. Care should be taken in choosing anticoagulants and keeping close follow-up in patients with high HCR rates.

LIMITATIONS

Since this study was designed retrospectively, full control over the data could not be achieved, and the limitations of our study include potential gaps in patient records. Additionally, the generalizability of the study results is limited due to the inability to access patient records from other centers. Since our study is a retrospective analysis, additional control over potential confounding effects related to the presence of DM could not be achieved. In future studies, using methods such as Propensity Score Matching to equalize groups with and without DM in larger sample sizes would be beneficial for enhancing comparability.

CONCLUSION

Our study was planned among patients with AF who had an ischemic attack. Although HCR has previously been found to be high in patients with CAD with extensive thrombus, no study has yet been conducted in patients with AF. HCR calculated from biochemical samples taken easily and cheaply in patients with AF and ischemic attack is the first study in this field and we believe that it will lead to other studies. We believe that calculating HCR may be predictive of ischemic events in patients with AF.

Within the limitations of our study, it seems to be single-centered. It needs to be supported by other multi-center studies with a larger number of patients.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Sefa Erdi Ömür;* ***Design:*** *Sefa Erdi Ömür;* ***Control/Supervision:*** *Emin Koyun;* ***Data Collection and/or Processing:*** *Ahmet Şimşek;* ***Analysis and/or Interpretation:*** *Sefa Erdi Ömür;* ***Literature Review:*** *Sefa Erdi Ömür;* ***Writing the Article:*** *Sefa Erdi Ömür;* ***Critical Review:*** *Emin Koyun;* ***References and Fundings:*** *Ahmet Şimşek;* ***Materials:*** *Ahmet Şimşek.*

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