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Clinical significance of CONUT score in atrial fibrillation patients aged 65 and over

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ABSTRACT

Objectives: The aim of this study was to examine the clinical importance of malnutrition in patients with non-valvular atrial fibrillation (AF) aged 65 and over who were receiving anticoagulant treatment and to distinguish the differences between direct oral anticoagulants (DOACs) and warfarin therapy.

Patients and methods: Between January 2016 and December 2020, a total of 423 AF patients (183 males, 240 females; mean age: 73.4±5.8 years; range, 65 to 89 years) were retrospectively analyzed. The patients were divided into two groups according to the Controlling Nutritional Status (CONUT) score: ≥5 (n=92) and <5 (n=331). All patients were followed for at least two years from the first presentation.

Results: Major bleeding and mortality were found to be higher in the CONUT score ≥5 group (8.7% *vs.* 3.0%, p=0.017 and 18.5% *vs.* 10.0%, p=0.025, respectively). While there was higher major bleeding and mortality in CONUT ≥5 patients using warfarin, there was no significant difference in the DOAC group (warfarin p=0.009, DOAC p=0.337 and warfarin p=0.046, DOAC p=0.171, respectively). In the receiver operating characteristic analysis, a cut-off value of 3.5 of the CONUT score predicted both mortality and major bleeding (area under the curve [AUC]: 0.781, p<0.001 and AUC: 0.733, p=0.001, respectively).

Conclusion: According to the CONUT score, a higher rate of major bleeding and mortality was found in AF patients aged 65 and over with moderate-severe malnutrition. Based on these findings, the use of DOAC may be more reliable in this patient group.

Keywords: Atrial fibrillation, major bleeding, malnutrition, mortality.

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population.[1] Its incidence increases with age, occurring in 4% of patients aged 65 years and over.[2] Serious complications such as heart failure, stroke and death may occur due to AF.[3,4] Older patients are more susceptible to nutritional deficiencies due to comorbidities and diseases.[5] Nutritional deficiencies have been studied in heart failure, malignancies, and chronic kidney disease and have been associated with mortality.[6,7] However, this has not been adequately studied in patients with AF. Screening middle-aged and elderly AF patients for nutritional deficiencies could be useful in developing individualized treatment modalities to improve patient prognosis.

The Controlling Nutritional Status (CONUT) score is an objective method that can be easily calculated from patients' laboratory data, such as albumin, total cholesterol and lymphocyte count, and indicates nutritional status.[8] Previous studies have shown that the CONUT score is useful for predicting prognosis in patients with coronary artery disease, heart failure, and transcatheter aortic valve implantation.[9-11] In a study conducted including patients hospitalized due to novel coronavirus disease 2019 (COVID-19), it was found that the CONUT score predicted in-hospital mortality.[12] In another study, malnutrition as assessed by the CONUT score was found to have a remarkable correlation with the incidence of bleeding and stroke in individuals with AF aged 80 years and older.[13]

In the present study, our primary objective was to investigate the effect of the CONUT score on clinical outcomes in patients with AF aged 65 years and older. Our secondary objective was to evaluate variations in anticoagulant selection.

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PATIENTS AND METHODS

Patient population

This two-center, retrospective study was conducted at Çermik State Hospital and Muş State Hospital, Department of Cardiology between January 2016 and December 2020. A total of 423 patients (183 males, 240 females; mean age: 73.4±5.8 years; range, 65 to 89 years) aged 65 and over with AF were included. The diagnosis of AF was made by 12-lead electrocardiography or 24-h rhythm Holter monitoring. Patients with valvular AF, malignancy, serious infection, not using anticoagulants, and whose CONUT score could not be calculated were excluded from the study.

Medical history, demographic data, medications, laboratory and echocardiographic results of each patient were collected retrospectively from the hospital electronic clinical information system. The patients' CHADS-VASC and HAS-BLED scores were calculated. All patients were using anticoagulant medication. In patients receiving vitamin K antagonists (VKAs), time in therapeutic range (TTR) was defined as the time during which the patients' international normalized ratio (INR) value was between 2 and 3. The TTR was calculated according to the Rosendaal method.[14] Patients with TTR >65% were considered to be receiving appropriate doses of warfarin. Patients with TTR <65% were excluded from the study. In patients receiving direct oral anticoagulants (DOACs), dose adjustment was adjusted according to the guideline recommendation.[15]

Evaluation of nutritional status

In our study, we used the CONUT score to assess nutritional status.[8] The CONUT score is calculated from serum albumin, total cholesterol and lymphocyte count (Table 1). According to the CONUT score, patients are categorized into four groups: normal (0-1), mild (2-4), moderate (5-8) and severe (9-12). In our study, patients were divided into two categories: normal-mild (0-4) and moderate-severe (≥5).

Follow-up

The primary outcome measures were ischemic stroke, major bleeding, and all-cause mortality. Ischemic strokes were characterized as clinical situations in which there was a sudden onset of neurological deficits that lasted at least 24 h, and this diagnosis was confirmed by computed tomography or magnetic resonance imaging. Major bleeding was determined according to the definition of the International Society on Thrombosis and Hemostasis (ISTH).[16] The records were reviewed over a period of at least two years from the first admission to the hospital for AF.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). Continuous data were expressed in mean ± standard deviation (SD) or median and interquartile range (IQR), while categorical data were expressed in number and frequency. The Kolmogorov-Smirnov test was utilized to assess the normality of the distribution for continuous variables. The Student t-test was applied for normally distributed variables, while the Mann-Whitney U test was employed for variables that did not follow a normal distribution. Categorical variables were compared using the chi-square test. Receiver operating characteristic (ROC) analysis was used to test the capacity of the CONUT score to predict mortality and major bleeding, as well as to determine a cut-off value based on the sum of the

Table 1
CONUT scoring system

	Normal	Mild	Moderate	Severe
Serum albumin (g/mL)	≥3.5	3.00-3.49	2.50-2.99	<2.5
Score	0	2	4	6
Total cholesterol (mg/dL)	≥180	140-179	100-139	<100
Score	0	1	2	3
Lymphocytes (counts/mL)	≥1,600	1,200-1,599	800-1,199	<800
Score	0	1	2	3

CONUT: Controlling nutritional status; Normal: 0-1; Mild: 2-4; Moderate: 5-8; Severe: 9-12.

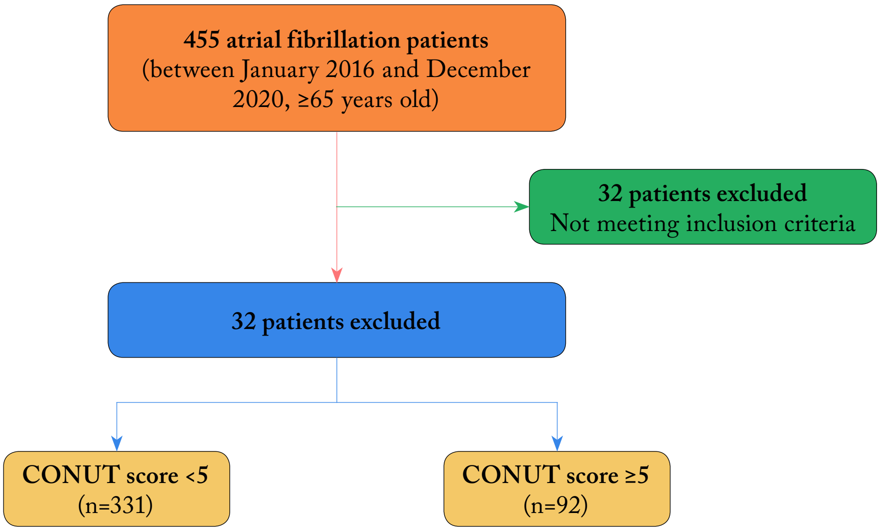

Figure 1. Study flowchart.
CONUT: Controlling nutritional status.

highest sensitivity and specificity. A *p* value of <0.05 was considered statistically significant.

RESULTS

There were 331 patients in the group with a CONUT score <5 and 92 patients in the group with a CONUT score of ≥5 (Figure 1). A statistically significant difference was found between the groups with respect to age and body mass index (BMI) (75.3±6.1 *vs.* 72.8±5.6 years, p<0.001 and 24.2±3.2 *vs.* 26.9±3.2 kg/m^2, p<0.001, respectively). The HAS-BLED and CHADS-VASC scores were similar in both groups. While creatinine was lower in the group with CONUT <5, there was no significant difference between other blood parameters (1.05 [0.84-1.57] *vs.* 0.95 [0.72-1.20], p<0.004). Additional comorbidities such as cardiomyopathy, chronic obstructive pulmonary disease, chronic renal failure, hypertension, and diabetes mellitus were present at a similar rate in each group. There was no significant difference in the choice of anticoagulant of the patients. There was a significant difference between the patient groups in terms of major bleeding and mortality (8.7% *vs.* 3.0%, p=0.017 and 18.5% *vs.* 10.0%, p=0.025, respectively). As a result, a higher rate of major bleeding and mortality was found in the group with a CONUT score of ≥5. On the other hand, the groups were similar in terms of ischemic cerebrovascular disease/ transient ischemic attack (CVD/TIA) (10.3 *vs.* 12.0%, p=0.643). The essential demographic characteristics of the patient cohort are outlined in Table 2.

The CONUT score was also evaluated in the DOAC and warfarin subgroups. Accordingly, major bleeding and mortality were significantly higher in patients with CONUT ≥5 in the warfarin subgroup, but no significant difference was found in the DOAC group (warfarin p=0.009, DOAC p=0.337 and warfarin p=0.046, DOAC p=0.171, respectively). In addition, there was no significant difference in terms of ischemic CVD/TIA in both subgroups according to the CONUT classification (warfarin p=0.223, DOAC p=0.760, respectively) (Figure 2).

Based on the ROC analysis, a cut-off value of 3.5 of the CONUT score predicted mortality with 72% sensitivity and 75% specificity (area under the curve [AUC]: 0.781, 95% confidence interval [CI]: 0.729-0.832, p<0.001) (Figure 3a). Similarly, in the ROC analysis, using this cut-off value, the CONUT score predicted major bleeding with 72% sensitivity and 71% specificity (AUC: 0.733, 95% CI: 0.635-0.831, p=0.001) (Figure 3b).

DISCUSSION

In the present study, we examined the effect of nutritional status, calculated using the CONUT score, on the clinical presentation of patients with AF aged 65 years and older taking oral anticoagulants. Patients with a CONUT score of ≥5 and classified

Table 2

Baseline demographic characteristics of patients

	CONUT score ≥5 (n=92)					CONUT score <5 (n=331)					
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	*p*
Age (year)			75.3±6.1					72.8±5.6			<0.001
Sex											
Female	53	57.6				187	56.5				0.849
Body mass index (kg/m^2)			24.2±3.2					26.9±3.2			<0.001
Heart rate (min)			85.2±16.4					86.9±18.1			0.416
Systolic blood pressure (mmHg)			129±16					128±17			0.717
Diastolic blood pressure (mmHg)			78.1±12.9					78.6±12.0			0.743
Ischemic CMP	32	34.8				96	29				0.286
COPD	17	18.5				77	23.3				0.329
GFR (mL/min)				59	29-73				59	38-72	0.388
BUN (mg/dL)				34	22-52				32	21-44	0.200
C reatinine (mg/dL)				1.05	0.84-1.57				0.95	0.72-1.20	0.004
Chronic renal failure	53	57.6				170	51.4				0.288
Hypertension	65	70.7				236	71.3				0.904
Diabetes mellitus	21	22.8				77	23.3				0.930
Ejection fraction				50	35-58				54	40-60	0.168
HAS-BLED score			1.83±0.84					1.88±0.94			0.647
CHA_2DS_2-VASC score			3.93±1.41					3.79±1.48			0.420
Warfarin	28	30.4				121	36.6				0.277
DOAC	64	69.6				210	63.4				0.277
CONUT score			6.34±1.17					2.35±0.98			<0.001
Ischemic CVD/TIA											
All	11	12.0				34	10.3				0.643
DOAC	5	7.8				19	9				0.760
Warfarin	6	21.4				15	12.5				0.223
Major bleeding											
All	8	8.7				10	3.0				**0.017**
DOAC	3	4.7				5	2.4				0.337
Warfarin	5	17.9				5	4.1				**0.009**
Mortality	17	18.5				33	10.0				**0.025**

CONUT: Controlling nutritional status; CMP: Cardiomyopathy; COPD: Chronic Obstructive Pulmonary Disease; GFR: Glomerular filtration rate; BUN: Blood urea nitrogen; DOAC: Direct oral anti coagulant; CVD/ TIA: Cerebrovascular disease/transient ischemic attack.

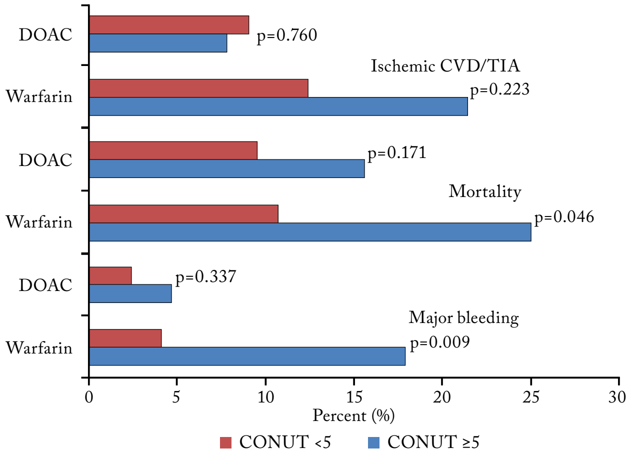

Figure 2. Evaluation of CONUT score in DOAC and warfarin subgroups.

CONUT: Controlling nutritional status; DOAC: Direct oral anticoagulants.

as moderate-severe malnutrition had a higher rate of major bleeding and mortality, and no significant difference was found in terms of ischemic stroke. While there was no significant difference in mortality and major bleeding according to nutritional status in patients taking DOAC, a higher rate of major bleeding and mortality was found in patients with moderate-to-severe malnutrition in the warfarin group.

Elderly individuals, particularly those with cardiovascular disease, often suffer from malnutrition. Based on previous research, it has been found that approximately 60 to 90% of malnourished elderly people are below a healthy weight.[17] Around 60 to 70% of elderly people who are considered frail are malnourished.[18] Malnutrition is not only a consequence of chronic diseases, but can also contribute to the progression of these diseases. Previous studies have demonstrated a link between malnutrition and unfavorable outcomes in patients with coronary artery disease or heart failure.[19,20] However, there are few studies investigating both the incidence and predictive significance of malnutrition in patients with AF.[21,22]

The BMI is a commonly used measure for evaluating nutritional status. However, its use is limited, particularly in patients with AF. This is because 21 to 68% of patients with AF have also heart failure.[23] In individuals with heart failure, the retention of sodium and water in the body can lead to weight gain, which can affect the accuracy of BMI as a measure. In addition, BMI is unable to

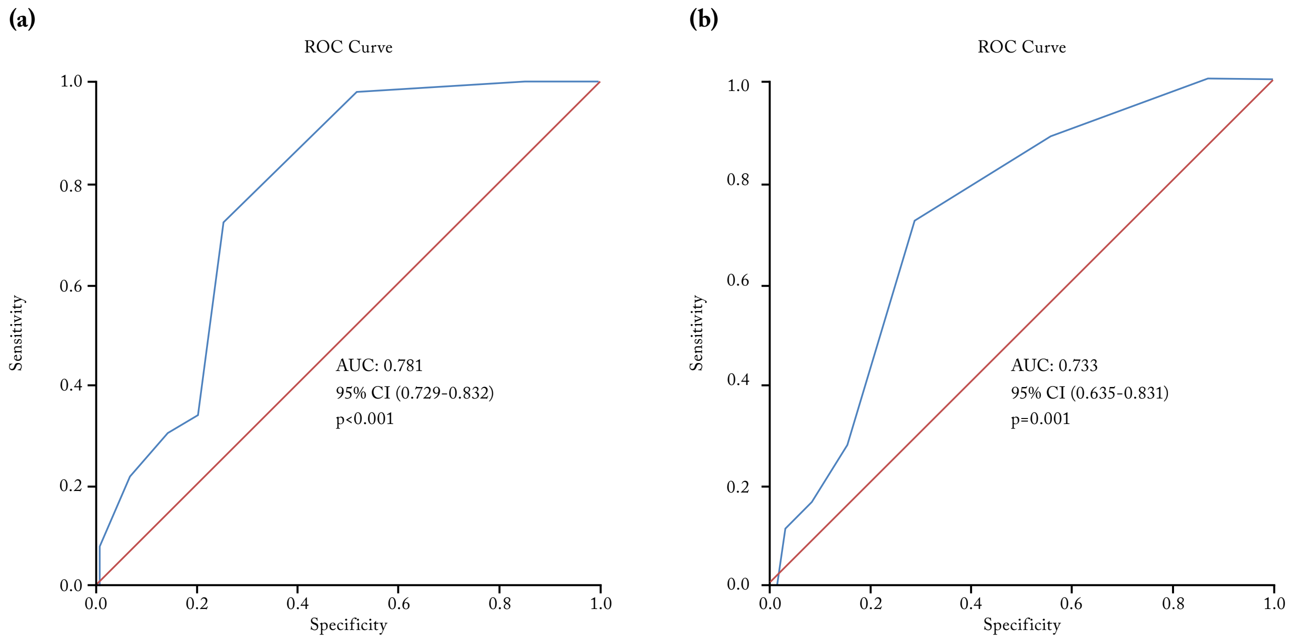

Figure 3. **(a)** ROC curve analysis of CONUT score on mortality in atrial fibrillation patients. **(b)** ROC curve analysis of CONUT score on major bleeding in atrial fibrillation patients.

ROC: Receiver operating characteristic; CONUT: Controlling nutritional status.

differentiate between muscle, fat and bone mass, and individuals with similar BMI values may have different metabolic profiles. The CONUT score is determined by measuring serum albumin, total cholesterol, and lymphocyte count. It serves as a comprehensive score that reflects the patient's frailty.

In our study, patients with a CONUT score of ≥5 were found to have a higher rate of major bleeding and mortality in the patient group receiving warfarin. However, no significant difference was observed between the groups in patients using DOAC. Polypharmacy often increases with age, as the prevalence of multiple health conditions or comorbidities increases. This situation increases the interaction of warfarin with other medications and, thus, it necessitates more frequent INR monitoring. Reduced muscle strength due to malnutrition limits physical activity and reduces hospital admissions.[24] This prevents regular follow-up and is one reason for the increase in the rate of major bleeding. Albumin level, one of the parameters in the CONUT score, is an important indicator reflecting nutritional status in clinical practice.[25] In addition, albumin levels also affect the efficacy of warfarin anticoagulation. Warfarin is completely absorbed after oral administration and subsequently binds to albumin in plasma to a high degree. The portion that remains unbound to albumin, about 1 to 10%, suppresses the synthesis of vitamin K-dependent coagulation factors in the hepatocytes, which leads to an anticoagulant effect. Previous studies have indicated increased anticoagulation and a higher risk of bleeding in individuals with low serum albumin levels receiving warfarin therapy.[26,27] These factors may explain the higher incidence of major bleeding and higher mortality in malnourished elderly AF patients taking warfarin in our study.

The assessment of malnutrition in patients with AF and the implementation of early interventions, particularly in patients with moderate to severe malnutrition, could have a significant impact on patient outcomes. Some studies have shown that the use of oral nutritional supplements and nutritional counseling can improve clinical outcomes in individuals with malnutrition.[28,29] The identification of malnutrition as an isolated risk factor for morbidity and mortality in elderly individuals with AF is important as malnutrition is a risk factor that can potentially be addressed and modified. Therefore, it is of great importance to develop a multidisciplinary team approach to reduce the negative effects of malnutrition in elderly patients with AF treated with anticoagulants. The recommendations of clinical nutritionists can play a crucial role in the development of a monitoring strategy. Incorporating oral nutritional supplementation can prove to be a valuable resource in preventing weight loss, enhancing nutritional health, and lowering complications in elderly AF patients suffering from malnutrition.

Nonetheless, there are some limitations to this study. The study was carried out in a retrospective manner at two centers, and the study sample size was relatively limited. In addition, we evaluated nutritional status exclusively at the moment of the initial hospital admission and did not explore any fluctuations or changes in nutritional status over the course of time. Therefore, it is not definitively established whether patients who had malnutrition at the beginning can maintain the same nutritional status, when they undergo clinical events. Finally, we only used the CONUT score to determine nutritional status. Therefore, we were not able to make a comparison with other nutritional scores with proven prognostic value.

In conclusion, the CONUT score is a critical measure used to evaluate the nutritional status of patients with AF. In our study, major bleeding and mortality rates increased, particularly in AF patients aged 65 and over who used anticoagulants and experienced moderate to severe malnutrition. We believe that the use of DOACs would be more appropriate in this patient group.

Ethics Committee Approval: The study protocol was approved by the Mardin Artuklu University Ethics Committee (date: 06.11.2023, no: 2023/11-20). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept, design, control/supervision, data collection and/or processing, analysis and/or interpretation, literature review, writing the article, critical review, references and fundings, materials: R.K.; Design, control/supervision, data collection and/or processing, literature review, critical review, references and fundings, materials: A.F.K.

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