Original Article

Evaluation of the Relationship between Cognitive Impairment and Atria Score Systems in Patients with Atrial Fibrillation

Emre Özdemir, Ayşen S. Ekinci[1], Sadık V. Emren, Simge Balaban[1], Muhammet M. Tiryaki, Mustafa Karaca, Enise N. Özlem Tiryaki[1], Cem Nazlı

Departments of Cardiology and [1]Neurology, Ataturk Research and Training Hospital, Izmir Katip Çelebi University, Izmir/Turkey

Abstract

Background: Atrial fibrillation (AF) is the main arrhythmia associated with thromboembolic complications and cognitive impairment. In this study, we aimed to evaluate the relationship between cognitive impairment and different scoring systems developed for AF to improve the medical follow-up of cognitive impairment. **Methods:** Between January 2019 and December 2020, 124 patients between the age of 30 and 80 years, diagnosed with AF for at least 5 years and complaining about memory impairment during cardiological follow-up, were included in the study. The patients were divided into two groups based on their cognitive status as assessed by the Mini-Mental State Examination group 1 consisted of 52 patients with cognitive impairment and group 2 comprised 72 patients without cognitive impairment. **Results:** The ATRIA bleeding score had a positive moderate correlation ($r = 0.454$, $P < 0.001$), the ATRIA stroke score had a strong correlation ($r = 0.738$, $P < 0.001$), and the SAMe-TT_2R_2 score had a strong correlation ($r = 0.688$, $P < 0.001$) with cognitive impairment. However, $CHADS_2$ and CHA_2DS_2VASc scores were not statistically correlated with cognitive impairment. According to the receiver operating characteristic (ROC) curve, the area under the curve (AUC) of the ATRIA bleeding score was 0.761 with a 95% confidence interval (CI) of 0.678–0.844 and $P < 0.001$; also, for the ATRIA stroke score, AUC was 0.930 with a 95% CI of 0.886–0.974 and $P < 0.001$. In addition, for the SAMe-TT_2R_2 score, AUC was 0.895 with a 95% CI of 0.838–0.952 and $P < 0.001$. In the pairwise comparison of AUC on ROC curves, the ATRIA stroke score and the SAMe-TT_2R_2 score were statistically similar ($P = 0.324$). ATRIA bleeding, ATRIA stroke, and SAMe-TT_2R_2 scores were greater than $CHADS_2$ stroke score (P: 0.0004, $P < 0.0001$, and $P < 0.0001$, respectively), but CHA_2DS_2-VASc and $CHADS_2$ stroke scores were statistically similar (P: 0.402). **Conclusion:** Both ATRIA stroke and SAMe-TT_2R_2 scoring systems can provide a better correlation than $CHADS_2$ and CHA_2DS_2-VASc scores in patients with AF to evaluate their cognitive status. These two scores can be more useful to monitor the patients with AF for medical follow-up of cognitive status.

Keywords: Atrial fibrillation, ATRIA score, cognitive impairment, CHA_2DS_2-VASc score, SAMe-TT_2R_2 score

Introduction

Cognitive impairment is associated with a deterioration of cognitive ability and independent living capacity, significantly affects quality of life.[1] Atrial fibrillation (AF) is a type of cardiac arrhythmia that causes irregular cardiac beats and thromboembolic complications.[2] Patients with AF face an increased risk of stroke, up to five-fold, due to thromboembolic complications.[3]

We know that stroke is the major vascular risk factor for cognitive impairment.[4] If AF is complicated with stroke, it becomes a risk factor and predictor of cognitive impairment and dementia.[5] Also, cognitive impairment and dementia are associated with brain ischemia and silent cerebral infarctions induced by AF.[6] AF may cause complications with cognitive impairment and dementia even in the absence of stroke.[7] A recent meta-analysis reported that there is an association between AF and cognitive impairment in patients without stroke, but this association is not stronger than in patients with stroke.[8] Potential factors like cerebral hypoperfusion, chronic inflammation, and endothelial dysfunction are believed to play a role in the pathogenesis of AF-associated cognitive impairment and dementia.[9]

Several studies have described the association between AF and cognitive impairment across different spectra. The association is independent of manifest stroke as well as of the several risk factors common to both AF and cognitive impairment, such as advanced age, congestive heart failure (CHF), diabetes mellitus (DM), arterial hypertension (AHT), atherosclerosis, and chronic kidney disease.[10]

The literature reveals that cognitive impairment and AF have similar risk factors. Furthermore, the development of stroke in AF is the most prominent cause of cognitive impairment. Therefore, the AF risk score systems which evaluate the risk of stroke in AF may be predictive of cognitive function.[10-13]

The $CHADS_2$ and CHA_2DS_2-VASc scores include these risk factors and these scores have been described to

Address for correspondence: Dr. Emre Özdemir, Katip Celebi University, Ataturk Education and Research Hospital, Izmir/Turkey.
E-mail: emreozdemir27@yahoo.com.tr

Submitted: 31-Jul-2023 **Revised:** 27-Nov-2023 **Accepted:** 29-Nov-2023
Published: 01-Feb-2024

DOI: 10.4103/aian.aian_674_23

select the patients who are at risk for stroke. The patients identified by these scores are most likely to benefit from oral anticoagulation (OAC).[11] Moreover, the prevalence of AF, which increases with comorbidities, shows a similar pattern in cognitive impairment.[12,13] Given these data, the relationship between cognitive impairment and various risk scores designed to evaluate the risk of stroke in AF is gaining interest.

Previous studies showed that the $CHADS_2$ and CHA_2DS_2-VASc scores can be useful in predicting cognitive impairment in patients with AF. Graves *et al*.[14] reported that cognitive impairment is associated with $CHADS_2$ and CHA_2DS_2-VASc scores. Liao *et al*.[15] showed the $CHADS_2$ and CHA_2DS_2-VASc scores can be estimated in AF patients for the risk of dementia. AlTurki *et al*.[16] demonstrated that there is a link among AF, cognitive impairment, and comorbidities.

As a newer stroke risk score, the ATRIA stroke score predicts stroke better than $CHADS_2$ and CHA_2DS_2-VASc scores.[17,18] Also, the most important factor for patients under anticoagulation is the time in therapeutic range (TTR) for international normalized ratio (INR). The SAMe-TT_2R_2 score uses a simple calculation and could potentially aid decision-making in the management of patients with AF.[19] According to the data that is related to $CHADS_2$ and CHA_2DS_2-VASc scores, there is a gap in evaluating the relationship between SAMe-TT_2R_2 and ATRIA scoring systems and cognitive impairment in the literature.

Considering this information, we aimed to evaluate the relationship between cognitive impairment using both SAMe-TT_2R_2 and ATRIA scoring systems in AF patients.

Methods

Study population: We collected data from January 2019 to December 2020 on 132 patients using oral anticoagulants who had complaints of memory impairment. Eight patients were excluded due to lack of data. Consequently, our study included 124 patients aged 30-80 years who were under cardiological follow-up, had complaints of memory impairment, had been using oral anticoagulants, and had been diagnosed with AF for at least 5 years. Our study population consisted of patients with a functional capacity similar to those who can attend routine follow-up. There were no disabled patients in our study.

Data collection: The Standard Mini-Mental State Examination (MMSE) cognitive function test was applied to literate patients, and the Modified Mini-Mental State Examination (MMSE-I) cognitive function test was used for illiterate patients. These tests comprise five subtests to assess orientation, attention/concentration, registration, recall, and language. MMSE and its subtests, which were developed for the literate and illiterate populations and are widely used all over the world, were analyzed as variables. The tests for validity and reliability of MMSE and MMSE-I tests had been performed for the Turkish population and were carried out as described in the literature.[20,21]

MMSE total score was categorized as follows: 24–30 points indicated normal cognitive function, 18–23 points indicated mild dementia, and 17 points or below indicated severe dementia. In the Memory section (3 points), which was the same for both literate and illiterate patients, three different words (blue, hawk, tulip) were told to the patient with a 1-s interval and they were asked to repeat them. If the patient could not say all of them in the first attempt, all the words were repeated up to two more times. Each correctly recalled word scored 1 point, regardless of the order of repetition. The patient was asked to recall these words right away. In the Attention section (5 points), illiterate patients were asked to count the days of the week backward. If the patient counted down a total of 5 days in sequence, 1 point was given for each correct day. For the literate patients, 1 point was given for each correct number when counting backward from 100 in threes. In our study, a MMSE/MMSE-I score under 24 points was accepted as a cut-off value to define cognitive impairment.

The ATRIA stroke risk score was originally developed to predict the risk of ischemic stroke in patients with AF. Major risk strata are determined by age and previous stroke history in this scoring system. In patients with or without prior stroke, the presence of CHF, DM, AHT, proteinuria, estimated glomerular filtration rate (eGFR) ≤45 mL/min/1.73 m^2 or dependent on dialysis, and female gender gives 1 point. Age ≥85 years gives 6 points, age 75-84 years gives 5 points, age 65-74 years gives 3 points, and age <65 years gives 0 points for patients without prior stroke; also, age ≥85 years gives 9 points, age 75-84 years gives 7 points, age 65-74 years gives 7 points, and age <65 years gives 8 points for patients with prior stroke.[17]

The ATRIA bleeding risk score was developed to detect the risk of hemorrhage associated with oral anticoagulant therapy. The score includes five variables: 3 points for anemia, 3 points for eGFR <30 mL/min/1.73 m^2 or dependent on dialysis, 2 points for age ≥75 years, 1 point for patients with prior bleeding, and 1 point for AHT.[22]

When OAC as an adjusted-dose vitamin K antagonist (VKA) is the selected treatment, the efficiency of anticoagulation therapy (the effective TTR of INR) is the main determinant of thromboembolism and bleeding. The SAMe-TT_2R_2 score includes the following criteria: sex (female), age (>60 years), medical history (more than two comorbidities of AHT, DM, coronary artery disease [CAD]/myocardial infarction, peripheral arterial disease, CHF, previous stroke, pulmonary disease, and hepatic or renal disease), and treatment (interacting drugs, e.g., amiodarone for rhythm control) receive 1 point and tobacco use (within 2 years) and race (non-white) receive 2 points. A SAMe-TT_2R_2 score of 0–1 indicates that VKA is optimal. A score of ≥2 suggests a risk of suboptimal anticoagulation control.[19]

Definitions were accepted as follows: hyperlipidemia (HPL) = regulated blood lipid levels with at least one drug or diet, DM = regulated blood glucose level with at least one drug or diet, AHT = regulated blood pressure with at least one

drug or diet, anemia = hemoglobin (Hb) levels <13 g/dL for males and <12 g/dL for females, and CHF = the status according to the New York Heart Association functional classification III/IV and/or a history of pulmonary edema. eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[23] Transient ischemic attack (TIA) was defined as a neurological dysfunction associated with focal cerebral ischemia, but without a permanent cerebral infarction. Stroke was accepted if neurological dysfunction was associated with a permanent cerebral infarction.

Data on serum creatinine (Cr), blood urea nitrogen (BUN), Hb, white blood cell (WBC), platelet (PLT), left ventricular ejection fraction (LVEF), and mitral valve stenosis (MS) grade were collected from hospital records and noted.

Patients were divided into two groups according to their cognitive status: group 1 consisted of 52 patients with cognitive impairment and group 2 included 72 patients without cognitive impairment.

Statistical analysis: Statistical analyses were performed with the Statistical Package for Social Sciences 15.0 software (SPSS, Chicago, IL, USA). Kolmogorov–Smirnov test was performed to assess whether the data had a normal distribution. Continuous variables were presented as mean (standard deviation [SD]) and/or median (interquartile range [IQR], Q1–Q3) values and were compared with a *t*-test and/or Mann–Whitney test depending on the type of data distribution. Categorical variables were presented as numbers and percentages. The Chi-square test was performed to compare categorical variables. The correlation between risk scores and cognitive function was evaluated using Spearman's rho test. The predictive value of the risk scores was determined using receiver operator analysis, and the area under the curve of the risk scores was compared using the DeLong test.[24] A value of $P < 0.05$ was considered statistically significant.

Approval for the study was granted by the local ethics committee, and informed consent was obtained from all patients.

Results

We collected data on 132 patients using oral anticoagulants and having complaints of memory impairment from January 2019 to December 2020. Eight patients were excluded because of lack of data. There were 52 patients in group 1 and 72 patients in group 2.

In our population, the mean age was 64.7 ± 10 years in group 1 and 67.9 ± 9.8 years in group 2 ($P = 0.094$). Group 1 had a male predominance (*n*: 27, 51.9%), while group 2 had a female predominance (*n*: 38, 52.8%) ($P = 0.605$). Persistent AF was the most frequent form of AF in group 2 ($P = 0.004$) [Table 1].

The mean (SD) values for group 1 were: Hb 12.9 (1.65) g/dL and WBC 8.3 (2.72)/L; the median (IQR) values were PLT 222 (88)/L, Cr 0.87 (0.37) mg/dL, BUN 14 (7) mg/dL, and LVEF 60 (10)%.[10] For group 2, the mean (SD) values were: Hb 12.9 (1.74) g/dL and WBC 7.7 (2.30)/L; the median (IQR) values were PLT 230 (108)/L, Cr 0.83 (0.24) mg/dL, BUN 15 (4) mg/dL, and LVEF 60 (5)% [Table 1].

In our study, AHT was the most frequent comorbid disease in both groups. There was no statistical difference between the two groups in terms of AHT and other variables (DM, HPL, smoking habit, stroke, TIA, mitral valve pathology). Similarly, there was no statistical difference between groups 1 and 2 in

Table 1: Clinical and laboratory variables of patients

Variable	Group 1 (*n*=52)	Group 2 (*n*=72)	*P*
Male gender, *n* (%)	27 (51.9)	34 (47.2)	0.605
Age (years), mean (SD)	64.7 (10.0)	67.9 (9.8)	0.094
Hb (g/dL), mean (SD)	12.9 (1.65)	12.9 (1.74)	0.527
WBC (/L), mean (SD)	8.3 (2.72)	7.7 (2.30)	0.227
PLT (/L), median (IQR)	222 (88)	230 (108)	0.629
Cr (mg/dL), median (IQR)	0.87 (0.37)	0.83 (0.24)	0.99
BUN (mg/dL), median (IQR)	14 (7)	15 (4)	0.720
LVEF (%), median (IQR)	60.0 (10)	60 (5)	0.573
Education status, *n* (%)			
Illiterates	7 (13.4)	17 (23.6)	0.264
Elementary school	25 (48.0)	38 (52.7)	
Junior high school	10 (19.2)	10 (13.8)	
High school	9 (17.3)	5 (6.9)	
University	1 (1.9)	2 (2.7)	
Persistent AF, *n* (%)	22 (42.3)	49 (68.1)	0.004
AHT, *n* (%)	37 (71.1)	55 (76.3)	0.511
DM, *n* (%)	10 (19.2)	17 (23.6)	0.560
CAD, *n* (%)	16 (30.7)	15 (20.8)	0.185
HPL, *n* (%)	14 (26.9)	23 (31.9)	0.546
Smoking, *n* (%)	9 (17.3)	3 (4.1)	0.16
Moderate–severe MS or mitral valve replacement, *n* (%)	11 (21.1)	17 (23.6)	0.362
Stroke, *n* (%)	4 (7.6)	9 (12.5)	0.388
TIA, *n* (%)	4 (7.6)	2 (2.7)	0.208

AF=atrial fibrillation, AHT=arterial hypertension, BUN=blood urea nitrogen, CAD=coronary artery disease, Cr=serum creatinine, DM=diabetes mellitus, Hb=hemoglobin, HPL=hyperlipidemia, IQR=interquartile range, LVEF=left ventricular ejection fraction, MS=mitral valve stenosis, PLT=platelet, SD=standard deviation, TIA=transient ischemic attack, WBC=white blood cell

Table 2: Spearman's rho test evaluation to compare the correlation of risk scores, education status, and cognitive impairment degree

Score system	Cognitive Impairment Degree Rho value	*P*
ATRIA bleeding	0.454	<0.001
ATRIA stroke	0.738	<0.001
SAMe-TT_2R_2	0.688	<0.001
$CHADS_2$	0.116	0.198
CHA_2DS_2VASc	0.163	0.70
Education status	-0.181	0.045

education status. The prevalence of patients with persistent AF was higher in group 2, which was the only significant statistical difference between the two groups ($P = 0.004$) [Table 1].

As shown in Table 1, there were four patients in group 1 and nine patients in group 2 who had experienced a stroke ($P = 0.388$). Of these, only two patients in group 2 had a hemorrhagic stroke, whereas the others in both groups had ischemic strokes. The clinical and imaging findings of the patients were heterogeneous.

Regarding the correlation with cognitive impairment, ATRIA bleeding score had a positive moderate correlation ($r = 0.454$, $P < 0.001$), ATRIA stroke score had a strong correlation ($r = 0.738$, $P < 0.001$), and SAMe-TT_2R_2 had a strong correlation ($r = 0.688$, $P < 0.001$) with cognitive impairment. Education status had a weak negative correlation ($r = –0.181$, $P = 0.045$). However, $CHADS_2$ and CHA_2DS_2-VASc scores did not demonstrate a statistically significant correlation with cognitive impairment [Table 2].

The receiver operating characteristic (ROC) curve of illustrating the correlation between cognitive impairment and risk scores is presented in Figure 1, and the area under the curve values in the ROC curve analysis are presented in Table 3.

For ATRIA bleeding score, with a cut-off point of >2.5 points, we could reach 70.8% sensitivity and 69.2% specificity, and for ATRIA stroke score with a cut-off point of >4.5 points, we could reach 86.1% sensitivity and 84.6% specificity. Similarly, for SAMe-TT_2R_2 score, with a cut-off point of >3.5 points, we could reach 87.5% sensitivity and 78.8% specificity [Table 4].

Discussion

To the best of our knowledge, this is the first study to evaluate ATRIA bleeding, ATRIA stroke, and SAMe-TT_2R_2 scores for predicting cognitive impairment in patients with AF and this study also compared these scores with the classic $CHADS_2$ and CHA_2DS_2-VASc scores.

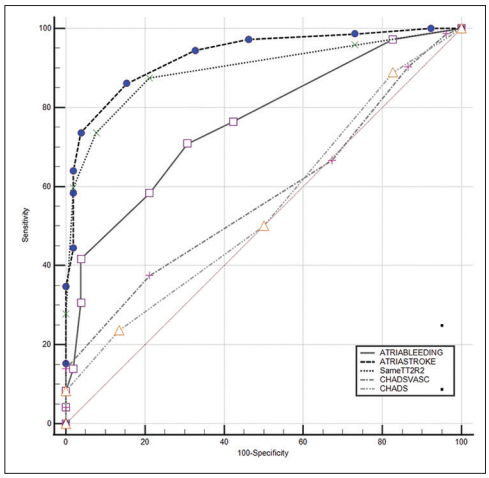

Figure 1: The ROC curve of correlation between cognitive impairment and risk scores. ROC = receiver operating characteristic

AF is the most common chronic cardiac arrhythmia with an increasing prevalence with age in the population.[2] We know that the presence of AF is associated with increased stroke risk, heart failure, and sudden death.

Cognitive impairment and dementia are primarily characterized by deterioration of cognitive ability and they significantly affect quality of life.[1] Nearly 35.6 million people lived with dementia in 2010, and this number is expected to nearly double every 20 years.[25] In recent years, several reports have shown an association between AF and cognitive functions, ranging from impairment to dementia.[26]

Cognitive impairment can be assessed using various validated tests. MMSE is one of the commonly used cognitive evaluation tests. MMSE is easy to use, does not require specialized equipment, and has a higher test–retest capacity. Nevertheless, its limitation lies in different education levels that is it may underestimate cognitive decline in educated patients.[27] The modified version of MMSE test, known as MMSE-I, has been well validated for use with illiterate patients.[21]

Brucki and Nitrini[28] reported that the MMSE scores correlated with educational level, and cognitive impairment may be underestimated in highly educated patients assessed by MMSE. In contrast to this finding, our study found no statistical differences between groups regarding education status; notably, illiterate patients were predominant among patients without cognitive impairment [Table 1]. Due to this homogeneity in our study, the comparison of risk scores and cognitive impairment in MMSE might become more effective.

AF increases the risk of stroke up to five-fold.[29] Stroke is associated with the risk of cognitive impairment and dementia.[30] AF can cause cognitive impairment without stroke; however, the relationship between AF and cognitive impairment in these patients is not completely understood. Potential mechanisms include microemboli, micro-bleeding, silent cerebral infarctions, subcortical white matter lesions, decreased cardiac output, and variable cerebral hypoperfusion

Table 3: AUC values in ROC curve analysis

Score system	AUC	95% Confidence interval	*P*
ATRIA bleeding	0.761	0.678–0.844	*P*<0.001
ATRIA stroke	0.930	0.886–0.974	*P*<0.001
SAMe-TT_2R_2	0.895	0.838–0.952	*P*<0.001
$CHADS_2$	0.546	0.444–0.648	0.378
CHA_2DS_2VASc	0.575	0.475–0.648	0.157

AUC=area under the ROC curve, ROC=receiver operating characteristic

Table 4: Cut-off values of scoring systems for cognitive impairment

Score system	Cut-off value	Sensitivity	Specificity
ATRIA stroke	>4.5	86.1%	84.6%
ATRIA bleeding	>2.5	70.8%	69.2%
SAMe-TT_2R_2	>3.5	87.5%	78.8%

from beat to beat for AF. In addition, there are some risk factors shared by both AF and cognitive impairment, such as CAD, hypertension and hypotension, heart failure, DM, and age.[31] AF and cognitive impairment have many common risk factors such as age, AHT, DM, and stroke.[32] Our study, similar to Graves *et al*.'s,[14] found no statistically significant differences in confounding factors, such as age, AHT, DM, stroke history and laboratory parameters had no statistical differences [Table 1].

In our study, although there was no statistical difference in the number of strokes between the groups, group 2 had a higher number of stroke patients. This finding aligns with the report of Graves *et al*.,[14] which indicated that the risk of dementia increases with higher $CHADS_2$ scores. Based on this information, it was thought that the risk score evaluation of patients might be more effective than assessing confounding conditions one by one.

In the current guidelines, patients with AF are considered to have the same thromboembolic risk for both persistent and paroxysmal AF.[11] However, a systematic review revealed that many studies have shown that AF duration is associated with cerebral perfusion, vascular dementia, and cognitive impairment, indicating that patients with paroxysmal AF and Sinus rhythm (SR) had better cognitive functions than those with persistent AF.[26] This data suggested that patients with AF who had no history of stroke can also be associated with cognitive impairment. Contrary to this finding, patients with persistent AF were higher in Group 2 [Table 1] in our study. We thought that this might be due to the random distribution of our study population.

The prediction of the possibility of thromboembolic events in AF is critical for morbidity, with $CHADS_2$, CHA_2DS_2-VASc, and ATRIA scores being used for nonvalvular AF.[33] Calculating these scores may help in protecting patients from having strokes, as well as from cognitive impairment and dementia in patients with AF. However, the fact that AF can be associated with cognitive impairment and dementia even in the absence of stroke has raised interest in the effectiveness of these risk scores in predicting cognitive impairment and dementia independent from stroke.

Graves *et al*.[32] showed that CHA_2DS_2-VASc scores are correlated with cognitive impairment and dementia. Similarly, Chou *et al*.[34] found that CHADS score is a potential tool to estimate the risk of dementia in patients with AF. Also, van den Ham *et al*.[33] reported that ATRIA risk score provided better results compared to $CHADS_2$ and CHA_2DS_2-VASc scores in predicting ischemic stroke. Based on these data, our study hypothesized that the ATRIA scoring systems, which evaluate ischemic events better than CHADS and CHADVASc, would better predict cognitive impairment. Consistent with our hypothesis, we found in our study that ATRIA stroke score and SAMe-TT_2R_2 score may be related to the cognitive status of patients. This finding can be supported when Graves *et al's*.,[32] Chou *et al's*.[34] Ham *et al's*.[33] findings are synthesized.

In the study of Graves *et al*.,[14] there was a male predominance of 54% and the mean age was 68.4 ± 13.8 years in patients with cognitive impairment, similar to our study.

In our population, 3.2% (*n*: 4) of patients had dementia in group 1, according to cognitive evaluation. This rate was lower than that reported by Singh-Manoux *et al.* (5.5%).[35] We observed cognitive impairment in 41.9% (*n*: 52) of our population, a rate that is nearly similar to 39% found in Koh *et al*.'s[36] review, but higher than that reported in Alonso *et al*.'s[37] study, which showed an increase of 20%–30% cognitive impairment in AF patients.

Moreover, Alonso *et al*.[37] demonstrated that the prevalence of cognitive impairment increased monotonically with a higher CHA_2DS_2-VASc score. In our study, however, we found no statistical correlation between CHA_2DS_2-VASc and $CHADS_2$ scores. On the other hand, we found that there were statistical correlations among ATRIA bleeding, ATRIA stroke, and SAMe-TT_2R_2 scores, with the strongest correlation found for the ATRIA stroke score [Table 3]. This finding aligns with the data reported by Aspberg *et al*.,[18] which indicated that ATRIA stroke score predicted ischemic stroke risk more effectively than $CHADS_2$ or CHA_2DS_2-VASc scores, and with Zulkifly *et al*.'s[38] data, which showed that the SAMe-TT_2R_2 score and the SAMe-TT_2R_2 score may be useful tools for patients under OAC in AF. Given the association of stroke with cognitive impairment, it is not unexpected that the ATRIA stroke and SAMe-TT_2R_2 scores show a higher correlation with cognitive impairment. Furthermore, labile TTR values may result in a decline in cognitive functions. In accordance with this, we found that the SAMe-TT_2R_2 score was associated with cognitive impairment.

As the main result of our study, we primarily found that ATRIA bleeding, ATRIA stroke, and SAMe-TT_2R_2 scores might be more closely associated and correlated with cognitive decline in patients with AF than the more frequently used $CHADS_2$ and CHA_2DS_2-VASc scores [Table 3 and Figure 1].

Within the limitations of our study outlined below, we identified potential cut-off values that may evaluate cognitive impairment for ATRIA bleeding, ATRIA stroke, and SAMe-TT_2R_2 scores [Table 4].

Limitations of the study

Our study has several limitations. First, the main limitation of our study was it being a retrospective study/having a one-center–based design. Second, it relied on a limited cognitive assessment using only one cognitive test. Third, there was a nonhomogeneous distribution of the confounding factors and AF duration (paroxysmal and persistent AF), which could lead to residual confounding. Fourth, our results require external validation before clinical application. To overcome all these limitations, prospective multicenter studies are needed.

Conclusion

In summary, our study suggests that the ATRIA and SAMe-TT_2R_2 scoring systems may provide a potential

predictive utility in evaluating cognitive impairment in patients with AF, compared to $CHADS_2$ and CHA_2DS_2-VASc scores. This data may be useful in patients with AF for medical monitoring of cognitive impairment. However, further studies with larger sample sizes and a prospective design are necessary to confirm our findings and provide external validation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: A systematic review and metaanalysis. Alzheimers Dement 2013;9:63–75.
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, *et al*. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: The Framingham Study. Stroke 1991;22:983–8.
4. Leys D, Henon H, Mackowiak-Cordoliani MA, Pasquier F. Poststroke dementia. Lancet Neurol 2005;4:752–9.
5. Pastori D, Miyazawa K, Lip GYH. Dementia and atrial fibrillation: A dangerous combination for ischemic stroke and mortality. J Alzheimers Dis 2018;61:1129-32.
6. Vermeer SE, Longstreth WT Jr, Koudstaal PJ. Silent brain infarcts: A systematic review. Lancet Neurol 2007;6:611-9.
7. Santangeli P, Di Biase L, Bai R, Mohanty S, Pump A, Brantes MC, *et al*. Atrial fibrillation and the risk of incident dementia: A meta-analysis. Heart Rhythm 2012;9:1761-8.
8. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: A meta-analysis. Ann Intern Med 2013;158:338–46.
9. Rivard L, Khairy P. Mechanisms, clinical significance, and prevention of cognitive impairment in patients with atrial fibrillation. Can J Cardiol 2017;33:1556-64.
10. Rivard L, Friberg L, Conen D, Healey JS, Berge T, Boriani G, *et al*. Atrial fibrillation and dementia: A report from the AF-SCREEN international collaboration. Circulation 2022;145:392-409.
11. Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomström-Lundqvist C, *et al*. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. Eur Heart J 2021;42:373-498.
12. Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features of chronic atrial fibrillation: The Framingham study. N Engl J Med 1982;306:1018-22.
13. Ding M, Qiu C. Atrial fibrillation, cognitive decline, and dementia: An epidemiologic review. Curr Epidemiol Rep 2018;5:252-61.
14. Graves KG, May HT, Jacobs V, Bair TL, Stevens SM, Woller SC, *et al*. Atrial fibrillation incrementally increases dementia risk across all CHADS2 and CHA2DS2VASc strata in patients receiving long-term warfarin. Am Heart J 2017;188:93-8.
15. Liao JN, Chao TF, Liu CJ, Wang KL, Chen SJ, Tuan TC, *et al*. Risk and prediction of dementia in patients with atrial fibrillation--A nationwide population-based cohort study. Int J Cardiol 2015;199:25-30.
16. AlTurki A, Maj JB, Marafi M, Donato F, Vescovo G, Russo V, *et al*. The role of cardiovascular and metabolic comorbidities in the link between atrial fibrillation and cognitive impairment: An appraisal of current scientific evidence. Medicina (Kaunas) 2019;55:767.
17. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, *et al*. A new risk scheme to predict ischemic stroke and other thromboembolism in atrial fibrillation: The ATRIA study stroke risk score. J Am Heart Assoc 2013;2:e000250. doi: 10.1161/JAHA.113.000250.
18. Aspberg S, Chang Y, Atterman A, Bottai M, Go AS, Singer DE. Comparison of the ATRIA, CHADS2, and CHA2DS2-VASc stroke risk scores in predicting ischaemic stroke in a large Swedish cohort of patients with atrial fibrillation. Eur Heart J 2016;37:3203-10.
19. Apostolakis S, Sullivan RM, Olshansky B, Lip GYH. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: The SAMe-TT2R2 score. Chest 2013;144:1555–63.
20. Güngen C, Ertan T, Eker E, Yaşar R, Engin F. The validity and reliability of the standardized mini-mental test in the diagnosis of mild dementia in Turkish Society. Turk Psikiyatri Derg 2020;13:273-81.
21. Babacan Yıldız G, Ur Özçelik E, Kolukısa M, Işık AT, Gürsoy E, Kocaman G, *et al*. The Validity and reliability study of the modified mini mental test for the uneducated (MMSE-E) in the diagnosis of Alzheimer's disease in Turkish Society. Turk Psikiatri Derg 2016;27:41-6.
22. Fang MC, Go AS, Chang Y, Borowsky LH, Pomernacki NK, Udaltsova N, *et al*. A new risk scheme to predict warfarin-associated hemorrhage: The ATRIA (Anticoagulation and Risk Factors in Atrial Fibrillation) Study. J Am Coll Cardiol 2011;58:395-401.
23. Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro III AF, Feldman HI, *et al*. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
24. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. Biometrics 1988;44:837-45.
25. Patterson C. World Alzheimer report 2018. London: Alzheimer's Disease International; 2018.
26. Gallinoro E, D'Elia S, Prozzo D, Lioncino M, Natale F, Golino P, *et al*. Cognitive function and atrial fibrillation: From the strength of relationship to the dark side of prevention. Is there a contribution from sinus rhythm restoration and maintenance? Medicina (Kaunas) 2019;55:587.
27. Cao L, Ha IS, Lin X, Shu D, Wang S, Yue J, *et al*. Comparison of the Saint Louis University mental status examination, the Mini-mental state examination, and the Montreal cognitive assessment in detection of cognitive impairment in Chinese elderly from geriatric department. J Am Med Dir Assoc 2012;13:626–9.
28. Brucki SMD, Nitrini R. Mini-mental state examination among lower educationl levels and illiterates: Transcultural evaluation. Dement Neuropsychol 2010;4:120-5.
29. Caplan LR. Atrial fibrillation, past and future: From a stroke non-entity to an over-targeted cause. Cerebrovasc Dis 2018;45:149–53.
30. Makin SD, Turpin S, Dennis MS, Wardlaw JM. Cognitive impairment after lacunar stroke: Systematic review and meta-analysis of incidence, prevalence and comparison with other stroke subtypes. J Neurol Neurosurg Psychiatry 2013;84:893-900.
31. Piccini JP, Hammill BG, SinnerMF, Hernandez AF, Walkey AJ, Benjamin EJ, *et al*. Clinical course of atrial fibrillation in older adults: The importance of cardiovascular events beyond stroke. Eur Heart J 2014;35:250–6.
32. Graves KG, May HT, Jacobs V, Knowlton KU, Muhlestein JB, Lappe DL, *et al*. CHA_2DS_2-VASc scores and intermountain mortality risk scores for the joint risk stratification of dementia among patients with atrial fibrillation. Heart Rhythm 2019;16:3-9.
33. van den Ham HA, Klungel OH, Singer DE, Leufkens HG, van Staa TP. Comparative performance of ATRIA, CHADS2, and CHA2DS2-VASc risk scores predicting stroke in patients with atrial fibrillation: Results from a national primary care database. J Am Coll Cardiol 2015;66:1851-9.
34. Chou RH, Chiu CC, Huang CC, Chan WL, Huang PH, Chen YC, *et al*. Prediction of vascular dementia and Alzheimer's disease in patients with atrial fibrillation or atrial flutter using CHADS2 score. J Chin Med Assoc 2016;79:470-6.
35. Singh-Manoux A, Fayosse A, Sabia S, Canonico M, Bobak M, Elbaz A, *et al*. Atrial fibrillation as a risk factor for cognitive decline and

dementia. Eur Heart J 2017;38:2612-8.
36. Koh YH, Lew LZ, Franke KB, Elliott AD, Lau DH, Thiyagarajah A, *et al*. Predictive role of atrial fibrillation in cognitive decline: A systematic review and meta-analysis of 2.8 million individuals. Europace 2022;24:1229-39.
37. Alonso A, Knopman DS, Gottesman RF, Soliman EZ, Shah AJ, O'Neal WT, *et al*. Correlates of dementia and mild cognitive impairment in patients with atrial fibrillation: The atherosclerosis risk in communities neurocognitive study (ARIC-NCS). J Am Heart Assoc 2017;6:e006014.
38. Zulkifly H, Lip GYH, Lane DA. Use of the SAMe-TT2R2 score to predict anticoagulation control in atrial fibrillation and venous thromboembolism patients receiving vitamin K antagonists: A review. Heart Rhythm 2018;15:615-23.