



The ATRIA score is superior to the m-CHA₂DS₂-Vasc score in predicting in-hospital mortality in COVID-19

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SUMMARY

OBJECTIVE: Coronavirus disease 2019 (COVID-19) has become a health and social problem all over the world. Most of the deaths occur from embolism and thrombus formation. We aimed to compare the predictive value of the anticoagulation and risk factors in atrial fibrillation (ATRIA) and m-CHA₂DS₂-Vasc scores in in-hospital mortality in COVID-19.

METHODS: Three-hundred and ninety-four patients who were hospitalized due to COVID-19 between 10 June 2020 and 10 September 2020 were included. Three-hundred and sixty patients who survived were defined as the non-mortality group and the remaining 34 whose hospitalizations resulted in death were defined as the mortality group. The anticoagulation and risk factors in atrial fibrillation and m-CHA₂DS₂-Vasc scores of the patients were calculated.

RESULTS: A total of 394 patients, mean age 66.2±9.7 (221 male [56.1%]) were included in this retrospective study. The median values of the anticoagulation and risk factors in atrial fibrillation and m-CHA₂DS₂-Vasc scores were different between the groups ($p < 0.000$ for both). The multivariate logistic regression analysis showed that both the m-CHA₂DS₂-Vasc and anticoagulation and risk factors in atrial fibrillation scores were independent predictors of in-hospital mortality ($p = 0.024$, 95%CI 1.039–1.704 for anticoagulation and risk factors in atrial fibrillation and $p = 0.043$, 95%CI 1.012–2.088 for m-CHA₂DS₂-Vasc). In the receiver operating characteristic curve analysis, the anticoagulation and risk factors in atrial fibrillation score was superior to the m-CHA₂DS₂-Vasc score with an AUC 0.774 and SE:0.037, and $p < 0.001$.

CONCLUSIONS: In our study, we showed that the anticoagulation and risk factors in atrial fibrillation and m-CHA₂DS₂-Vasc scores can be used as predictors of thrombosis and mortality in COVID-19 patients. In addition, the predictive value of the anticoagulation and risk factors in atrial fibrillation score was higher than that of m-CHA₂DS₂-Vasc. The use of the anticoagulation and risk factors in atrial fibrillation score to assess high-risk patients in COVID-19 may be recommended.

KEYWORDS: Anticoagulants. Risk score. Coronavirus.

INTRODUCTION

The mortality rate of COVID-19, which emerged in Wuhan, China in the last quarter of 2019, varies between 2–3%¹⁻². This rate can go up to 50% in those who are hospitalized in intensive care units³. Possible complications of COVID-19, a viral infection, can be listed as septic shock, acute cardiac injury,

arrhythmia, cardiovascular collapse, ARDS, and multiple organ failure⁴. Although most of the fatal cases included patients who died due to respiratory failure, in addition to this outcome, myocardial damage or heart failure findings were observed in some cases^{5,6}. In COVID-19 patients, it is stated that the risk for coagulopathy increases especially in the elderly, or those

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with comorbid diseases, due to endothelial damage caused by the virus that binds to ACE₂, endothelial damage due to sepsis, activation of inflammatory and microthrombotic mechanisms, and stasis due to prolonged hospitalization^{7,8}. Considering that thromboembolism increases mortality, the importance of determining which patients are at a greater risk for thromboembolism can be clearly justified. Congestive heart failure-Hypertension-Age ≥ 75 years-Diabetes Mellitus-Stroke (CHADS₂), Congestive heart failure-Hypertension-Age ≥ 75 years-Diabetes Mellitus-Stroke-Vascular disease-age 65–74 years- female sex (CHA₂DS₂-Vasc), modified-Congestive heart failure-Hypertension-Age ≥ 75 years-Diabetes Mellitus-Stroke-Vascular disease-age 65–74 years- male sex (m-CHA₂DS₂-Vasc) and the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) scores are the most common scoring systems used to determine the risk of these patients^{9,10}. In a study conducted by Kılıc et al., it was emphasized that the CHADS₂-Vasc score was a predictor of unsuccessful response in STEMI patients receiving thrombolytic therapy¹¹. Studies have shown that the ATRIA score is superior to CHADS₂ and CHADS₂-Vasc in predicting the risk for thromboembolism^{12,13}. Cetinkal et al. showed in their recently published studies that mortality increases in COVID-19 patients with higher m-CHA₂DS₂-Vasc scores¹⁴. The aim of this study was to compare the ATRIA and m-CHA₂DS₂-Vasc scores in patients with COVID-19 who were followed in intensive care units.

METHODS

This retrospective study consisted of 394 patients who were hospitalized with COVID-19 symptoms and laboratory or radiological findings between 10 June 2020 and 10 September 2020. Additionally, all patients over the age of 18 who had a confirmed diagnosis of HT, DM, and other comorbid conditions and received ongoing treatment were included in the study. Patients with end-stage heart failure, malignancy, chronic inflammatory disease, and known coagulopathy were excluded. In the study of Ai et al., published in August, chest CT findings were more sensitive than PCR positivity¹⁵. Considering that, PCR positivity status was not imposed for the patients included in our study. A detailed medical history was recorded for each patient, and the baseline clinical characteristics at study entry, along with information on follow-up, were carefully collected. Systolic heart failure was defined as left ventricular ejection fraction $< 40\%$. Hypertension was defined as systolic and diastolic blood pressures $> 140/90$ mmHg or if the patient was taking any anti-hypertensive medication. Diabetes mellitus (Type 2 DM) was defined as having a previous diagnosis of DM or using an anti-diabetic medication, or fasting blood glucose

≥ 126 mg/dL or HbA1c $> 6.5\%$. Patients with a history of thromboembolic stroke originating from carotid or vertebral arteries were defined as “presence of stroke”. m-CHA₂DS₂-Vasc score was calculated by adding 2 points for age ≥ 75 years; 2 points for prior stroke or transient ischemic attack (TIA); and 1 point for each of the following factors: congestive heart failure or left ventricular ejection fraction $\leq 40\%$, hypertension, diabetes mellitus, vascular disease, age 65–74, and male gender, with a maximum score of 9 points¹⁴. The ATRIA risk score was calculated by adding 1 point for each of the following factors: female gender, diabetes mellitus, congestive heart failure, hypertension, proteinuria, and renal dysfunction (i.e. eGFR < 45 mL/min/1.73 m² or end-stage renal disease), and by adding 0–9 points depending on the specific score weight of patient’s age according to the presence or absence of prior ischemic stroke¹⁶. We did not have data about proteinuria, so the maximum score of the ATRIA risk score will be 14 points. Patients with ≤ 5 points were defined as low risk, patients with 6 points were at intermediate risk, while patients with ≥ 7 points were defined as high risk¹⁷.

eGFR was estimated using the 4-variable Modification of Diet in Renal Disease (MDRD-4) equation¹⁸.

The study was approved by the Clinical Research Ethics Committee of the Ministry of Health of our country and the local Clinical Research Ethics Committee of our hospital (No. 1081, date: September 23, 2020). The study protocol complies with the ethical guidelines of the 1975 Declaration of Helsinki, as reflected in the approval previously obtained by the institution’s human research committee.

Statistical analysis

All statistical analyses were performed with SPSS 17 (SPSS, Inc., Chicago, Illinois, USA) and MedCalc for Windows. The minimum number of subjects required in both groups for a significant difference between the two groups was 40 for the ATRIA score and 41 for the m-CHA₂DS₂-Vasc score (type 1 error: 0.01, test power: 0.9). Continuous variables were expressed as mean \pm standard deviation (mean \pm SD) or median (interquartile range), and categorical variables as numbers and percentages. Comparisons of the continuous variables between groups were performed using the independent samples t-test and Mann-Whitney U test. For appropriate and categorical variables, the χ^2 test or Fisher’s exact test was used. We analyzed whether continuous variables had normal distribution using the Kolmogorov-Smirnov test. Univariate and multivariable logistic regression analyses were performed to assess the relationship between the ATRIA and m-CHA₂DS₂-Vasc scores. Variables with a $p \leq 0.05$ in univariate analysis were included in the multivariate analysis. The receiver operating characteristic

(ROC) curve analysis was performed to demonstrate the cut-off values, and sensitivity and specificity of the ATRIA and m-CHA₂DS₂-Vasc scores in showing COVID-19 mortality. The results are expressed as relative risk and 95% confidence interval (CI). A p value lower than 0.05 was considered statistically significant.

RESULTS

Three-hundred and ninety-four patients with a mean age of 66.2±9.7 years were included in the study (56.1%, n=221, male). Three-hundred and two patients (n=15, mortality group) were in the low-risk category, 49 (n=8, mortality group) were in the intermediate-risk category, and 43 (n=11, mortality group) were in the high-risk category according to the ATRIA score. One-hundred and ninety-six (n=5, mortality group) patients had a m-CHA₂DS₂-Vasc score of <3 and the remaining 198 (n=29, mortality group) had a score of ≥3. The median ATRIA and m-CHA₂DS₂-Vasc scores, with which patient-based cumulative risk was calculated and total comorbidity was evaluated, were different between the groups (Table 1).

A multivariate logistic regression analysis showed the ATRIA and m-CHA₂DS₂-Vasc scores were independent predictors of mortality in COVID-19 patients. Moreover, in the ROC analysis, the ATRIA score performed better than the m-CHA₂DS₂-Vasc score at predicting mortality with an AUC 0.774, 95%CI 0.729–0.814 and SE:0.037, and p<0.001 (Figure 1). The results of univariate and multivariate logistic regression analyses are shown in Table 2.

DISCUSSION

COVID-19 has become a health problem with deaths worldwide. It is known that mortality is higher in the elderly and those with comorbidity and widespread pulmonary involvement¹⁹. Around

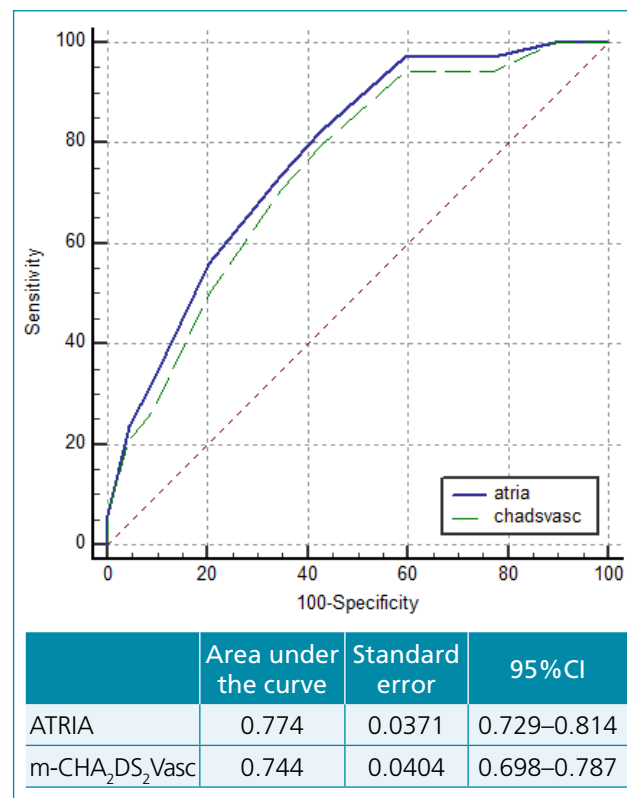


Figure 1. Receiver operating characteristic curve analysis of the ATRIA and m-CHA₂DS₂Vasc scores.

Table 1. Baseline characteristics of non-mortality and mortality groups.

	Non-mortality group (n=360)	Mortality group (n=34)	p
Age, years	65.8±9.9	70.3±6.3	0.009*
Gender, male, n(%)	202 (56.1)	19 (55.8)	0.980
HT, n (%)	228 (63.3)	27 (79.4)	0.063
DM, n (%)	129 (35.8)	17 (50)	0.136
CAD, n (%)	117 (32.5)	16 (47)	0.091
HF, n (%)	31 (8.6)	6 (17.6)	0.115
CVD, n (%)	6 (1.6)	2 (5.8)	0.146
ESRD or GFR<45, n (%)	9 (2.5)	0 (0)	1.000
AF, n (%)	16 (4.4)	1 (2.9)	1.000
m-CHA ₂ DS ₂ -VAsc, median (IQR)	2 (0–6)	5 (1–7)	<0.001
ATRIA, median (IQR)	3 (0–8)	6 (1–10)	<0.001

AF: atrial fibrillation; ATRIA: the anticoagulation and risk factors in atrial fibrillation; CAD: coronary artery disease; CVD: history of cerebrovascular disease; DM: diabetes mellitus; ESRD: end-stage renal disease; GFR: glomerular filtration rate; HF: heart failure; HT: hypertension; m-CHA₂DS₂Vasc: modified-congestive heart failure-hypertension-age ≥75 years-diabetes mellitus-stroke-vascular disease-age 65–74 years-sex category;

*Although p-value was statistically significant, lowest and highest age values were in the same score for both scoring systems.

Table 2. Univariate and multivariate regression analyses of the ATRIA and m-CHA₂DS₂-VAsc scores, and other variables.

	Univariate analysis OR (95% CI)	p	Multivariate analysis OR (95% CI)	p
ATRIA score	1.603 (1.339–1.920)	<0.001	1.331 (1.039–1.704)	0.024
m-CHA ₂ DS ₂ -VAsc score	1.976 (1.529–2.554)	<0.001	1.453 (1.012–2.088)	0.043
Age	1.012 (1.052–1.093)	0.010	–	–

ATRIA: the anticoagulation and risk factors in atrial fibrillation; m-CHA₂DS₂-VAsc: modified-congestive heart failure-hypertension-age ≥75 years-diabetes mellitus-stroke-vascular disease-age 65-74 years-sex category.

5–10% of the patients who have the disease become severely ill and need intensive care²⁰. While the mortality rate in intensive care hospitalizations reaches 60% when the disease was first detected, it is now around 20%. The course of the disease is more serious and mortality rates are higher in those who are intubated²¹.

Increased vasoconstrictor angiotensin II, decreased vasodilator angiotensin, and sepsis-induced release of cytokines can trigger a coagulopathy in COVID-19²². It is known that approximately 50% of patients hospitalized due to COVID-19 develop thrombosis and, despite anticoagulation, a high number of patients with ARDS secondary to COVID-19 followed in intensive care unit developed life-threatening thrombotic complications²³.

Determining the thrombosis risk of the patients who are followed in intensive care units due to COVID-19 is important to both improve disease prognosis and guide treatment. Coagulation tests, such as prothrombin time, fibrinogen, activated partial thromboplastin time and fibrin degradation product, and d-dimer, are the laboratory tests that could determine patients' coagulation status^{24,25}. Zhang et al. showed that elevated d-dimer levels on admission could predict in-hospital mortality in patients with COVID-19²⁶. In another study by Tang et al., longer prothrombin time and higher levels of d-dimer and fibrin degradation product were determined in non-survivors²⁷. Similar to these results, we determined higher levels of d-dimer and longer prothrombin time in patients with COVID-19 who did not survive.

The CHA₂DS₂-Vasc score, which is one of the most widely used scoring systems to determine thrombosis risk without the need for laboratory tests, has been evaluated in recent studies in patients with COVID-19. Çetinkal et al. demonstrated that higher CHA₂DS₂-Vasc scores are associated with adverse clinical events in patients with COVID-19, and they also showed that the m-CHA₂DS₂-Vasc score was superior to the CHA₂DS₂-Vasc score in predicting in-hospital mortality. The ATRIA score is another score used for thrombosis risk and some studies have indicated it performs better at determining risk compared to the CHA₂DS₂-Vasc score. In our study, where we compared the ATRIA and m-CHA₂DS₂-Vasc scores, we found that both scores were higher in non-survivors. Also, we believe

both scores can be used as independent predictors of thrombosis and mortality in patients hospitalized in intensive care units due to COVID-19. In addition, the predictive value of the ATRIA score was higher than that of the m-CHA₂DS₂-Vasc score. A relationship between COVID mortality and CHA₂DS₂-Vasc has been shown in previous studies²⁸. ATRIA may have a better performance than m-CHA₂DS₂-Vasc as it categorizes age more effectively and is calculated using GFR.

Acute pulmonary embolism, deep-vein thrombosis, ischemic stroke, myocardial infarction, and systemic arterial embolism are responsible for the majority of deaths in COVID-19 patients. Although the treatment protocol of these patients includes anticoagulants, there is no definite consensus on dosage. Identifying patients at risk of thromboembolism could offer the possibility of more careful treatment in the form of thromboprophylaxis. The ATRIA score could be a guide in determining whether anticoagulants can be used in prophylactic or therapeutic doses in this group.

We think that the low number of patients in our study is a limitation that can be overcome with a longer study period and prospective studies. The fact that the laboratory parameters affecting the prognosis of COVID-19 infection were not obtained is not a great obstacle to our study, as it will only play a role in proteinuria evaluation in the ATRIA score, which we already mentioned in the protocol and did not add to the study.

Limitations

Our study has more than one limitation. The most significant one is the retrospective and single-centered design of the study. Furthermore, since there were no data for proteinuria, it was evaluated as 0 in all patients included in the study. The laboratory parameters that could have an effect on the primary outcome were not included in the study, and this is another limitation.

CONCLUSIONS

The ATRIA and CHA₂DS₂-Vasc scores are scoring systems that can be used to determine the risk of thromboembolism in

COVID-19 patients and can be evaluated quickly at bedside. Moreover, the ATRIA score may give a better result than the CHA₂DS₂-Vasc score. It can be recommended for the evaluation of high-risk COVID-19 patients.

AUTHORS' CONTRIBUTIONS

OOA: Conceptualization, Data curation, Formal analysis, Supervision, Writing – original draft. **AY:** Data curation, Formal analysis, Supervision.

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