Original Article

Comparative Performance of CHA2DS2VASc and AnTicoagulation and Risk Factors in Atrial Fibrillation Risk Scores for Predicting Mortality in Patients with COVID-19

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Abstract

Background: The AnTicoagulation and Risk factors in Atrial fibrillation (ATRIA) and CHA_2DS_2VASc risk scores used to detect the thromboembolic and hemorrhagic risk in atrial fibrillation (AF) patients has been shown recently to predict poor clinical outcomes varies clinical settings, regardless of having AF. We aimed to examine the potential utility of admission CHA_2DS_2VASc and ATRIA scores for predicting in-hospital mortality in patients with coronavirus disease 2019 (COVID-19). **Methods:** In this retrospective study hospitalized 134 COVID-19 patients who diagnosed with a positive polymerase chain reaction test, were included. Patients were divided into two groups who were died and survivors, both the groups were compared according to clinical, laboratory, and demographic features, including the CHA_2DS_2VASc and ATRIA risk score. Predictors of mortality were determined by logistic regression analysis. **Results:** ATRIA and CHA_2DS_2VASc risk scores were predicting mortality in COVID-19 patients. Logistic regression analysis showed that ATRIA risk score, AF and chronic obstructive pulmonary disease were an independent predictor of mortality. For an ATRIA score cut off value of 3, the sensitivity was 77.78%, specificity 57.94%, positive predictive value 31.80, and negative predictive value 91.20. For a CHA_2DS_2VASc score cut-off value of 4, the sensitivity was 44.44%, specificity 83.18%, positive predictive value 40, and negative predictive value 85.60. **Conclusion:** CHA_2DS_2VASc and ATRIA scores can be used as a novel, simple tool for predicting mortality in COVID-19 patients.

Keywords: Atrial, coronavirus, embolism, fibrillation, mortality

Introduction

The outbreak of the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread throughout the world.[1]

When infected with SARS-CoV-2, patients with preexisting hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), cerebrovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and kidney dysfunction have worse clinical outcomes than those without them.[2]

COVID-19 may predispose both venous and arterial thromboembolic diseases due to excessive inflammation, hypoxia, immobilization, and diffuse intravascular coagulation.[3-6] Precise knowledge of the incidence of thrombotic complications in COVID-19 patients is essential for decision-making about the intensity of thromboprophylaxis, especially in patients admitted to the intensive care unit who are at the highest thrombotic risk.[7]

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In the practice of cardiology, simple clinical risk scores have been used to define the risks in different clinical settings, such as atrial fibrillation (AF). The CHA_2DS_2VASc (Congestive heart failure [CHF], HT, age, diabetes, previous stroke/transient ischemic attack [TIA], vascular disease, and sex category [female gender]) risk score has been recommended by the guidelines for stroke risk stratification and further guides the optimization of anticoagulation therapy in patients with nonvalvular AF.[8,9] In recent years, the use of the CHA_2DS_2VASc score in predicting ischemic stroke, thromboembolism, and death has extended beyond the original disease state for which it was proposed.[10,11] Current studies have shown that the more recently developed AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) RS determine the predisposition to thromboembolic and hemorrhagic events in AF, which demonstrates better accuracy than the CHA_2DS_2VASc score in predicting ischemic stroke.[12-14] This score is a newly proposed stroke risk-stratification tool derived from the ATRIA cohort and validated in the external ATRIA-Cardiovascular (CV) Research Network cohort.[15]

With the spread of SARS-CoV-2 and a rise in the number of cases, an increasing number of SARS-CoV-2-infected patients exhibit comorbidities such as HT, diabetes, and cardiac and CVDs.[16] Depending on the inflammatory reaction, the entire microvascular system may be damaged, leading to abnormal activation of the coagulation system, which pathologically represents vasculitis and microthrombosis.[17,18]

Although the mortality rate in COVID-19 infection is not high, SARS-CoV-2 is highly contagious, and the rapidity of the spread of the infection has resulted in a pandemic. Therefore, risk-scoring systems are important for clinicians in managing and treating and predicting mortality in infected patients.

In this study, we aimed to examine the potential utility of admission CHA_2DS_2VASc and ATRIA scores in predicting the in-hospital mortality in patients with COVID-19.

Methods

In this retrospective, single-center study hospitalized, COVID-19 patients aged 18 years and above who underwent a positive polymerase chain reaction (PCR) test at diagnosis between March 28, 2020, and April 25, 2020, were included. The patients' demographic characteristics, relevant clinical data, comorbidities, and biochemical markers were obtained from the hospital's electronic database. HT was defined as receiving antihypertensive treatment or systolic pressure >140 mm Hg and/or diastolic pressure >90 mm Hg on at least 2 separate measurements during hospitalization.[19] DM was defined as taking oral antidiabetic agents or insulin or follow-up fasting blood glucose levels ≥126 mg/dL in accordance with the criteria of the American Diabetes Association.[20] Hyperlipidemia was defined as taking lipid-lowering medications on presentation.[21] Chronic kidney disease (CKD) was considered in the presence of an estimated glomerular filtration rate (GFR) 3 months, with or without kidney damage.[22] CHF and CAD were defined based on a previous data. The CHA_2DS_2VASc and ATRIA scores of each patient were calculated.

The CHA_2DS_2VASc score was calculated by allotting one point each for CHF, HT, DM, age between 65 and 74 years, female gender, and vascular disease two points each for age ≥75 years and a history of stroke or TIA. The risk factors assessed in the ATRIA risk score are shown in Table 1.

COVID-19 patients aged 18 years and above who underwent a positive PCR test at diagnosis were enrolled into the study. Patients who have malignancy, pregnancy, and insufficient data were excluded from the study.

The local ethics committee approved the study protocol (2020/175) and the study was carried out according to the principles of the Declaration of Helsinki (2013).

Ethical statement

Bakırkoy Dr. Sadi Konuk Educational and Research Hospital committee approved the study protocol (2020/175) and the study was carried out according to the principles of the Declaration of Helsinki (2013).

Statistical analysis

Statistical analysis of the variables was performed using SPSS version 20.0 (IBM corp., Armonk, NY, USA). Descriptive statistical methods (mean, standard deviation [SD], median, frequency, percentage, and minimum and maximum) were used for evaluating the study data. The distribution of variables was tested using the Shapiro–Wilk test and by graphical examination. Student's *t*-test was used for the comparison between two groups with the normal distribution of quantitative variables, and the Mann–Whitney *U*-test was used for the comparison between two groups with nonnormally distributed quantitative variables. Quantitative variables are expressed as mean ± SD, median ± interquartile range, or median (minimum/maximum), while categorical variables are expressed as *n* (%). Pearson's Chi-square test and Fisher's exact test were used to comparing qualitative data. Diagnostic

Table 1: Risk factors used in anticoagulation and risk factors in atrial risk score

Risk factor	Points without prior stroke	Points with prior stroke
Age (years)		
>85	6	9
75-84	5	7
65-74	3	7
<65	0	0
Female	1	1
DM	1	1
CHF	1	1
HT	1	1
Proteinuria	1	1
eGFR <45 or ESRD	1	1

eGFR: Estimated glomerular filtration rate, ESRD: End-stage renal disease, CHF: Congestive heart failure, DM: Diabetes mellitus, HT: Hypertension

screening tests (sensitivity, specificity, polycystic kidney disease, and nonspesific kidney disease), a receiver operating characteristic (ROC) curve analysis, and the exact binomial test were used to determine the predictive values of the parameters. The confidence level (CI) for the variables was set at 95%, with $P < 0.05$ deemed statistically significant. We used logistic regression analysis for evaluating the effects of variables such as age, HT, DM, CAD, CHF, AF, COPD, and chronic renal failure, CHA_2DS_2VASc and ATRIA scores, GFR, c-reactive protein (CRP), procalcitonin, D-dimer, troponin with $P < 0.05$ on mortality.

Results

Data of 261 patients were evaluated. Patients whose electronic data could not be obtained and pregnant women were excluded from the study. Overall, 134 patients were included in the final analysis. The mean age was 60.78 ± 13.12 (19–91) years, and 67% ($n = 90$) were male. Baseline clinical characteristics of patients in relation to mortality are presented in Table 2. The incidence of HT, CAD, CHF, AF, COPD were statistically higher in deceased patients ($P = 0.005$, $P = 0.007$, $P = 0.003$, $P = 0.026$, $P = 0.033$). No statistically significant differences were found in terms of age, gender, smoking status, diabetes, hyperlipidemia, CKD, and CVD ($P > 0.05$) [Table 2]. The mortality causes of the deceased patients were acute respiratory failure in 20 (74%) patients, pulmonary embolism in 3 (11%) patients, myocardial infarction in 4 (15%) patients.

The serum creatine kinase–myocardial band, aspartate aminotransferase, alanine aminotransferase, calcium (Ca), phosphorus (P), magnesium (Mg), sodium (Na), potassium (K), ferritin, platelet, and monocyte measurements did not show significant differences in relation to mortality ($P > 0.05$).

Table 2: Demographic and baseline clinical characteristics of coronavirus disease-19 patients

	Total (%)	Survivors (%)	Nonsurvivors (%)	*P*
Age, mean±SD	60.78±13.12	59.92±13.53	64.22±10.90	0.128[a]
Gender				
Female	44 (32.8)	33 (30.8)	11 (40.7)	χ^2: 0.958
Male	90 (67.2)	74 (69.2)	16 (59.3)	0.328[b]
Smoking	5 (12.5)	4 (10.5)	1 (50.0)	0.237[c]
HT	72 (53.7)	51 (47.7)	21 (77.8)	0.005**,[b]
Diabetes	38 (28.4)	27 (25.2)	11 (40.7)	0.110[b]
Hyperlipidemia	12 (9.0)	9 (8.4)	3 (11.1)	0.707[c]
CAD	25 (18.9)	15 (14.3)	10 (37.0)	0.007**,[b]
Heart failure	12 (9.0)	5 (4.7)	7 (25.9)	0.003**,[c]
AF	4 (3.0)	1 (0.9)	3 (11.1)	0.026*,[c]
COPD	7 (5.3)	3 (2.9)	4 (14.8)	0.033*,[c]
CKD	16 (12.0)	10 (9.4)	6 (22.2)	0.094[c]
CVD	3 (2.3)	3 (2.8)	0	1.000[c]

[a]Student *t*-test, [b]Pearson Chi-square test, [c]Fisher's exact test, *P<0.05, **P<0.01. COPD: Chronic obstructive pulmonary disease, SD: Standard deviation, CKD: Chronic kidney disease, CAD: Coronary artery disease, HT: Hypertension, AF: Atrial fibrillation, CVD: Cerebrovascular disease

However, the troponin, urea, creatinine, triglyceride, lactate dehydrogenase, CRP, procalcitonin, activated partial thromboplastin time, D-dimer, white blood cell, and lymphocyte levels of deceased patients were found to be significantly higher than those of survivors (all $P < 0.01$). The GFR and Hg values of deceased patients were significantly lower than those of survivors ($P = 0.001$, $P = 0.004$, respectively). The patients' biochemical parameters are summarized in Table 3.

While the mean ATRIA score of the deceased patients was 4.3, it was found to be 2.79 for the survivors. The ATRIA score of deceased patients was significantly higher than that of survivors. ($P = 0.003$). The mean CHA_2DS_2VASc score was 2.9 for deceased patients and 1.8 for survivors. The CHA_2DS_2VASc score of the patients who died was significantly higher than that of survivors ($P = 0.001$) [Table 4].

The effects of the age, ATRIA score, CHA_2DS_2VASc score and the presence of HT, DM, CAD, CHF, AF, COPD, and CKD, troponin, GFR, CRP, procalcitonin, D-Dimer on mortality were evaluated using logistic regression analysis; the model was found to be significant, and the explanatory coefficient was good (87.3%) [Table 5]. While the CHF, COPD, CKD, GFR, CRP, and procalcitonin were found to be independent risk factors that had a significant effect on mortality ($P < 0.05$), the effects of the other variables were not significant ($P > 0.05$). CHF ([odds ratio (OR)]: 50,374; 95% CI: 6.18–410,78; $P = 0.000$), CKD ([OR]: 0,113; 95% [CI]: 0.01–0.935; $P = 0.043$), and COPD ([OR]: 31.170 (%95 CI: 3.454–281.31; $P = 0.002$) were associated with an increased risk of mortality in COVİD-19 patients. The effect of one unit increase in GFR, CRP, procalcitonin on mortality increased the OR by 0.963 (95% CI: 0.940–0.986), 1.007 (95% CI: 1.001–1.013), 1.111 (95% CI: 1.042–1.182) times, respectively [Table 5].

Based on the ROC curve analysis, the cut-off point obtained for the ATRIA score was determined as 3, the sensitivity was 77.78%, specificity 57.94%, positive predictive value 31.80, and negative predictive value 91.20, area under the curve (AUC) value was 0.686 (95% CI: 0.588–0.784, $P = 0.003$). The cut-off point obtained for the CHA_2DS_2VASc score was determined as 2, the sensitivity was 77.78%, specificity 48.60%, positive predictive value 27.63, and negative predictive value 89.66, AUC value was 0.706 (95% CI: 0.603–0.809, $P = 0.039$) [Figure 1].

Discussion

The current study, both the ATRIA and CHA_2DS_2VASc RS were statistically higher in deceased patients with COVID-19. Our study also demonstrated that the ATRIA RS was similar to the CHA_2DS_2VASc RS in determining in-hospital mortality. Both scores demonstrated a high negative predictive value for mortality in COVİD-19 patients.

The CHA_2DS_2VASc and ATRIA risk scores were mainly developed and validated to estimate the risk of thromboembolism

Table 3: Laboratory findings of patients

	Mean±SD			*P*
	Total	Survivor (*n*=107)	Nonsurvivor (*n*=27)	
CKMB (U/L)	8.64±13.02	6.95±10.71	11.69±16.25	0.422[d]
Troponin (ng/ml)	1320.05±7958.93	666.83±3018.38	3836.19±16503.02	0.001**,[d]
Urea (mg/dl)	51.77±34.2	45.49±28.84	76.63±42.27	0.001**,[d]
Creatinine (mg/dl)	1.31±1.46	1.21±1.4	1.7±1.66	0.008**,[d]
GFR (ml/min/1.73m^2)	80.24±31.79	85.02±29.09	61.3±35.42	0.001**,[a]
Triglycerides (mg/dl)	149.39±105.41	138.37±85.15	199.5±163.18	0.004**,[d]
AST (UL)	160.63±733.47	107.83±343.11	369.85±1488.31	0.128[d]
ALT (IUL)	80.52±372.02	46.75±83.41	214.33±810.14	0.126[d]
LDH (UL)	373.95±184.64	341.27±143.6	503.44±261.76	0.002**,[d]
CRP (mg/L)	100.37±94.72	86.9±86.69	153.75±107.46	0.001**,[d]
Ferritin	810.03±1763.4	737.97±1917.6	810.03±932.31	0.059[d]
Procalcitonin (ng/ml)	3.15±10.33	1.15±4.59	11±19.4	0.001**,[d]
aPTT (sn)	40.43±17.36	38.88±17.28	46.66±16.58	0.013*,[d]
D-dimer (µgFEU/ml)	1.56±3.66	1.19±3.53	2.97±3.89	0.001**,[d]
WBC (10e3/uL)	8.22±4.8	7.38±4.37	11.54±5.03	0.001**,[d]
Hemoglobin (g/dl)	11.66±2.14	11.93±2.06	10.6±2.18	0.004**,[a]
PLT (10e3/uL)	226.81±101.57	232.58±105.60	204.15±81.70	0.429[d]
Lymphocyte	1.81±3.76	1.61±2.06	2.62±7.33	0.005**,[d]

[a]Student *t*-test, [b]Mann-Whitney U-test, **P*<0.05, ***P*<0.01. CK-MB: Creatine kinase-myocardial band, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase, CRP: C-reactive protein, aPTT: Activated partial thromboplastin time, WBC: White blood cell, SD: Standard deviation, PLT: Platelet

Table 4: Comparison of anticoagulation and risk factors in atrial fibrillation and CHA_2DS_2VASc scores between two groups

	Total	Survivor	Nonsurvivor	*P*
ATRIA				
Minimum-maximum (median)	0-8 (2)	0-8 (2)	1-8 (4)	0.003**
Mean±SD	3.09±2.57	2.79±2.57	4.30±2.25	
CHA_2DS_2VASc				
Minimum-maximum (median)	0-5 (2)	0-5 (2)	1-5 (3)	0.001**
Mean±SD	2.01±1.49	1.79±1.44	2.89±1.40	

**P*<0.05, ***P*<0.01. Student *t*-test, Pearson Chi-square test. SD: Standard deviation, ATRIA: Anticoagulation and risk factors in atrial fibrillation

in patients with nonvalvular AF.[23] Singer *et al*. reported that the ATRIA RS showed a better performance than the CHA_2DS_2VASc score in predicting ischemic stroke, especially in the low-risk group,[24] and similar results have also been reported in different patient cohorts.[25,26] However, in some studies, the opposite results have been shown.[27-29]

In the COVID-19 pandemic, the pulmonary complications have been the primary focus of healthcare providers, but they need to be aware of the CV and thromboembolic complications, which can be substantial contributors to the mortality associated with this disease.[30,31] SARS-CoV-2 not only causes viral pneumonia but also has a major impact on the CV system. Patients with CV risk factors including the male sex, an advanced age, the presence of DM, HT, or obesity, as well as patients with established CV and CVDs have been identified as particularly vulnerable populations at an increased risk of morbidity and mortality from COVID-19. Moreover, a considerable proportion of patients may develop a cardiac injury in the context of COVID-19, which portends an increased risk of in-hospital mortality.[32]

Therefore, in this study, our objective was to estimate the risk of mortality in COVID-19 patients using these risk-scoring tools. Although both these scores were developed for predicting thromboembolic events in patients with AF, based on different studies and the current guidelines, their constituent components such as old age, DM, renal dysfunction, heart failure, and prior vascular disease are common predictors of poor prognosis in patients having COVİD-19.[33]

In this study, CHF, CKD, COPD, GFR, CRP, and procalcitonin were found to be independent risk factors for mortality, and the effects of the other variables on mortality were not significant. The other principal finding in this study was that both CHA_2DS_2VASc and ATRIA RS of the patients who died were significantly higher than those of survivors. We demonstrated that a CHA_2DS_2VASc score of 2 can be used as a cut off value with a sensitivity of 77.78% and a specificity of 48.60%, and an ATRIA score of 3 can be used as a cut off value with a sensitivity of 77.78% and a specificity of 57.94%.

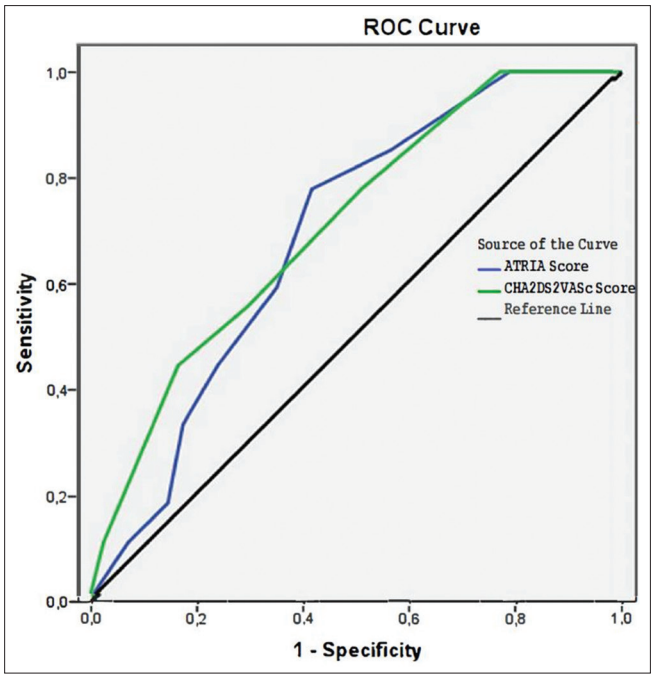

Figure 1: Receiver operating characteristic curve analysis, for the AnTicoagulation and Risk factors in Atrial fibrillation and CHA_2DS_2VASc score. For an AnTicoagulation and Risk factors in Atrial fibrillation score cut-off value of 3, the sensitivity was 77.78%, specificity 57.94%, positive predictive value 31.80, and negative predictive value 91.20. For a CHA_2DS_2VASc score cut-off value of 4, the sensitivity was 44.44%, specificity 83.18%, positive predictive value 40, and negative predictive value 85.60

Table 5: Logistic regression analysis for mortality

	P	95% CI, odds	Odds lower	Odds upper
Age	0.148	0.943	0.870	1.021
HT	0.746	1.384	0.193	9.948
Diabetes	0.126	3.535	0.703	17.790
CAD	0.071	6.828	0.845	55.148
CHF	0.000**	50.374	6.177	410.787
AF	0.114	18.663	0.494	704.868
COPD	0.002**	31.170	3.454	281.319
CKD	0.043*	0.113	0.014	0.935
Troponin	0.483	1.000	1.000	1.000
GFR	0.002**	0.963	0.940	0.986
CRP	0.018*	1.007	1.001	1.013
Procalcitonin	0.001**	1.111	1.044	1.182
D-dimer	0.861	0.989	0.869	1.124
ATRIA score (≥3)	0.096	7.206	0.705	73.636
CHA_2DS_2VASc (≥2)	0.415	0.353	0.029	4.324

*P<0.05, **P<0.01. ATRIA: Anticoagulation and risk factors in atrial fibrillation, CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, GFR: Glomerular filtration rate, CRP: C-reactive protein, CKD: Chronic kidney disease, CAD: Coronary artery disease, CHF: Congestive heart failure, HT: Hypertension, AF: Atrial fibrillation

Previous studies have investigated the clinical application and the importance of these scores in various clinical settings. One study demonstrated that the CHA_2DS_2VASc risk score could be an independent predictor of no-reflow in patients with ST-elevation myocardial infarction (STEMI).[34] Other studies that evaluated the potential value of the CHA_2DS_2VASc score in predicting the risk of adverse CV outcomes among patients with acute coronary syndrome showed that an elevated CHA_2DS_2VASc score was independently associated with increased in-hospital and long-term mortality.[35-37] A recent study on the association between CHA_2DS_2VASc scores and acute stent thrombosis in patients with stable CAD and acute coronary syndrome, a score of 3 or more had an independent predictive value for acute stent thrombosis.[38]

Furthermore, Aksoy and Bagcı demonstrated that the ATRIA and CHA_2DS_2VASc scoring systems were useful in detecting contrast-induced nephropathy following STEMI.[39]

In terms of the applicability of the CHA_2DS_2VASc and ATRIA scores in routine clinical practice for patients with COVID-19, data presented here may help health professionals to identify high-risk patients based on their CHA_2DS_2VASc and ATRIA scores. It is important for clinicians to be aware of these comorbidities when treating patients with COVID-19 as such patients are more likely to require critical care.

Limitations

This study has some limitations. The sample size was relatively small, we have insufficient data such as electrocardiographic parameters, blood pressure, body mass index, oxygen saturate, drugs on admission and the study was conducted using data from a single center. Although COVID-19 is associated with thromboembolic complications, and both scores have mainly been developed to assess these events, we did not specifically investigate any thrombotic events and reported all-cause mortality instead. According to the suggestions of the Turkish Society of Cardiology's Consensus Report on the COVID-19 Pandemic and CVDs, transthoracic echocardiography (TTE) was not performed routinely in all COVID-19 patients. Therefore, echocardiographic data could not be obtained for all patients. TTE was only performed in 26 patients.

Conclusion

We believe that the CHA_2DS_2VASc and ATRIA scores, which can be easily implemented in day-to-day clinical practice, may serve as simple yet effective tools for predicting high risk patients with COVID-19.

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Conflicts of interest

There are no conflicts of interest.

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