Evaluation of Modified ATRIA Risk Score in Predicting Mortality in Hospitalized Patients With COVID-19

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ABSTRACT

Background: As the Modified Anticoagulation and Risk Factors in Atrial Fibrillation Risk Score (M-ATRIA-RS) encompasses prognostic risk factors of novel coronavirus-2019 (COVID-19), it may be used to predict in-hospital mortality. We aimed to investigate whether M-ATRIA-RS was an independent predictor of mortality in patients hospitalized for COVID-19 and compare its discrimination capability with CHADS, CHA2DS2-VASc, and modified CHA2DS2-VASc (mCHA2DS2-VASc)-RS.

Methods: A total of 1,001 patients were retrospectively analyzed and classified into three groups based on M-ATRIA-RS, designed by changing sex criteria of ATRIA-RS from female to male: Group 1 for points 0−1 ($n = 448$), Group 2 for points 2−4 ($n = 268$), and Group 3 for points ≥ 5 ($n = 285$). Clinical outcomes were defined as in-hospital mortality, need for high-flow oxygen and/or intubation, and admission to intensive care unit.

Results: As the M-ATRIA-RS increased, adverse clinical outcomes significantly increased (Group 1, 6.5%; Group 2, 15.3%; Group 3, 34.4%; $p < 0.001$ mortality for in-hospital). Multivariate logistic regression analysis showed that M-ATRIA-RS, malignancy, troponin increase, and lactate dehydrogenase were independent predictors of in-hospital mortality ($p < 0.001$, per scale possibility rate for ATRIA-RS 1.2)**.** In receiver operating characteristic (ROC) analysis, the discriminative ability of M-ATRIA-RS was superior to mCHA2DS2-VASc-RS and ATRIA-RS, but similar to that Charlson Comorbidity Index (CCI) score ($AUC_{M-ATRIA}$ vs AUC_{ATRIA} Z-test=3.14 $p = 0.002$, $AUC_{M-ATRIA}$ $vs.$ $AUC_{mCHA2DS2-VASc}$ Z-test=2.14, $p = 0.03$; $AUC_{M-ATRIA}$ $vs.$ AUC_{CCI} Z-test=1.46 $p = 0.14$).

Conclusions: M-ATRIA-RS is useful to predict in-hospital mortality among patients hospitalized with COVID-19. In addition, it is superior to the mCHA2DS2-VASc-RS in predicting mortality in patients with COVID-19 and is more easily calculable than the CCI score.

Key Indexing Terms: SARS-CoV-2; COVID-19; ATRIA risk score; Risk stratification; Mortality. **[Am J Med Sci 2021;362 (6):553−561.]**

INTRODUCTION

Novel coronavirus-2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), has been recently emerged and rapidly spread to the world, resulting in a devastating pandemic.[1,2] Patients may present with a wide range of symptoms from asymptomatic infection to severe pneumonia accompanied by multisystemic failure which can lead to death, eventually.[3] Several studies have demonstrated that COVID-19 is associated with adverse clinical outcomes and a higher mortality rate in males, elderly, and those having comorbidities such as hypertension, cardiovascular disease, diabetes, chronic respiratory disease, and chronic kidney disease.[1,4,5] Scoring systems are developed to identify high-risk patients for the development of adverse events during COVID-19.[6]

Both the CHA2DS2-VASc and Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) risk scores are

cost-effective and simple scoring systems used to predict the risk of thromboembolism in non-valvular atrial fibrillation (AF) patients.[7,8] Patients with COVID-19 are usually at high risk for thromboembolic events.[9] Components of the scoring systems such as advanced age, presence of hypertension, and presence of diabetes mellitus (DM) are also prognostic risk factors for COVID-19. Cetinkal et al.[10] demonstrated that modified CHA2DS2-VASc score (mCHA2DS2-VASc), was designed by changing the sex variable of CHA2DS2-VASc score from female to male, was a useful tool for predicting prognosis in COVID-19 patients. In another study, the CHA2DS2-VASc-RS was found to predict in-hospital mortality in COVID-19 patients, regardless of AF.[11] Recent studies have shown that the ATRIA-RS, which has been more recently developed to identify the predisposition to thromboembolic events in AF, can predict ischemic stroke better than the CHADS and CHA2DS2-VASc scores.[8,12,13] However, the value of ATRIA and modified ATRIA-RS (M-ATRIA-RS), in which the sex criterion was changed from female to male, in predicting prognosis in patients with COVID-19 still remains to be elucidated.

In the present study, we aimed to investigate whether M-ATRIA-RS was an independent predictor of mortality in patients hospitalized for COVID-19 and compare its discrimination capability with CHADS, CHA2DS2-VASc, and mCHA2DS2-VASc-RS.

MATERIALS AND METHODS

This retrospective study included a total of 1001 patients diagnosed with COVID-19 at Istanbul Medeniyet University and Goztepe Prof. Dr. Suleyman Yalcin City Hospital and Umraniye Training and Research Hospital, Departments of Cardiology and Infectious Diseases and Clinical Microbiology, Istanbul, Turkey between March 20th, 2020 and November 20th, 2020. Those having pregnancy or severe frailty based on the attending physician's discretion were excluded from the study. Demographic and clinical characteristics of the patients including age, sex, presence of hypertension, DM, hyperlipidemia, previous cardiovascular disease, congestive heart failure, chronic obstructive pulmonary disease (COPD), previous cerebrovascular disease, and length of hospital stay and laboratory test results were retrieved from the medical records of the hospital database. Atrial fibrillation was defined as having both paroxysmal and chronic AF. A written informed consent was obtained from each patient. The study protocol was approved by the Istanbul Medeniyet Univercity and Goztepe Prof. Dr. Suleyman Yalcin City Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

For renal failure and proteinuria, laboratory records were used in addition to diagnostic codes. Renal dysfunction was defined as an estimated glomerular filtration rate of <60 ml/min/1.73 m^2 or previously diagnosed renal failure.[14] The laboratory data included the first week of

hospitalization consisting of biochemical parameters and complete blood count analysis.

Scoring systems

The ATRIA-RS, in which age and prior stroke are considered the major risk factors, was originally developed to predict the risk of ischemic stroke in patients with AF. When the ATRIA-RS is calculated in patients with prior stroke, age is more heavily weighted in the scoring system. The ATRIA-RS of the entire study population is calculated based on whether there is a prior stroke (Table 1).[8]

The CHADS-RS is calculated by assigning one point for each factor such as age >75 years, hypertension, DM, and congestive heart failure and two points for a history of transient ischemic attack (TIA) and/or stroke. The CHA2DS2-VASc score is calculated by assigning one point for each factor such as age between 65 and 74 years, hypertension, congestive heart failure (ejection fraction <40%), DM, vascular disease (*e.g.*, myocardial infarction or peripheral arterial disease), and female sex and two points for age >75 years and history of stroke or TIA.[7] The sex criterion of the ATRIA and CHA2DS2-VASc scores was arbitrarily switched from female to male, as the male sex was reported as an important predictor of mortality in COVID-19 patients according to recent reports.[1] Thus, we attempted to improve the predictive ability of the ATRIA and CHADS2-VASc scores for mortality. These novel scoring systems were named as the M-ATRIA and mCHA2DS2-VASc.

The Charlson Comorbidity Index (CCI) is a validated scoring system to classify each patient based on 19 medical conditions. One point is assigned for each comorbidity component (*i.e.*, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, chronic pulmonary disease, rheumatologic disease, dementia, peptic ulcer disease,

Table 1. Risk factors used in ATRIA-RS.

Risk factor	Points without prior stroke (points)	Points with prior stroke (points)
Age, years		
>85	6	9
75—84	5	7
65—74	3	7
<65	0	0
Female sex	1	1
DM	1	1
CHF	1	1
Hypertension	1	1
Proteinuria	1	1
eGFR <45 mL/min/ 1.73 m^2 or ESRD	1	1

ATRIA-RS: Anticoagulation and Risk Factors in Atrial Fibrillation Risk Score; DM: diabetes mellitus; CHF: congestive heart failure; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease.

DM, or mild liver disease); 2 points to cerebrovascular (hemiplegia) event, diabetes with chronic complications, cancer without metastases, and moderate-to-severe renal disease; 3 points to moderate or severe liver disease; and 6 points to metastatic solid tumors or full-blown acquired immunodeficiency syndrome (AIDS; zero point was set in this study, as our dataset contained no AIDS patients).[15]

The study population was classified into three groups according to their M-ATRIA scores as follows: Group 1 ($n = 448$), 0−1; Group 2 ($n = 268$), 2−4; and Group 3 ($n = 285$), ≥5. Adverse clinical outcome measures were defined as the need for invasive mechanical ventilation (intubation), intensive care unit (ICU) admission, and in-hospital mortality.

Statistical analysis

Statistical analysis was performed using the SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in median and inter-quartile range (IQR) or number and frequency. The normality of the distribution was analyzed using the Kolmogorov−Smirnov test. One-way analysis of variance (ANOVA) with Tukey and Bonferroni *post-hoc* analyses or Kruskal−Wallis test and chi-square test were used to compare the study groups based on the M-ATRIA-RS tertiles for continuous variables and categorical variables, respectively. A logistic regression analysis was used to identify independent predictors of in-hospital mortality. The receiver operating characteristic (ROC) analysis was used to determine the predictive accuracy and performance of the M-ATRIA-RS, ATRIA-RS, CHA2DS2-VASc-RS, mCHA2DS2-VASc-RS, CHADS-RS, and CCI for in-hospital mortality. These ROC curves were compared using the De-Long method. A goodness-of-fit test was calculated using the Hosmer-Lemeshow test and differences between the model-predicted and observed event rates were determined. C statistics were calculated to assess of the predictive ability of the model used in logistic regression analysis. A *p* value of <0.05 was considered statistically significant with 95% confidence interval (CI).

RESULTS

Demographic and clinical characteristics of the patients and laboratory data are summarized in Tables 2 and 3, respectively. The patients in the high M-ATRIA-RS tertile were older with a more frequent history of DM, hypertension, hyperlipidemia, stroke, heart failure, AF, chronic kidney disease, proteinuria ($p<0.001$, for all), COPD ($p = 0.004$), cardiovascular disease ($p = 0.006$), and malignancy ($p = 0.16$). Troponin I, creatine kinase-myocardial band (CK-MB), glucose, urea, creatinine, C-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH) ($p<0.001$, for all), alanine aminotransferase ($p = 0.003$), aspartate aminotransferase ($p = 0.001$), D-dimer ($p = 0.002$), and ferritin levels ($p = 0.004$) tended to

increase progressively from a lower M-ATRIA to higher M-ATRIA tertile. However, hemoglobin levels, and lymphocyte and neutrophil counts decreased from a lower M-ATRIA to a higher M-ATRIA tertile ($p<0.001$). The median length of hospital stay was 7 (4−12) days, 8 (5−12) days, and 9 (5−14) days in Group 1, Group 2, and Group 3, respectively ($p<0.001$). The choice of in-hospital medications was similar among the groups, except for favipiravir and ritonavir therapy ($p<0.001$ and $p = 0.004$, respectively). The high M-ATRIA tertile was significantly associated with a higher prevalence of adverse events compared to the other two groups. The rates of in-hospital mortality, ICU admission, and requirement for invasive mechanical ventilation of the groups are illustrated in Fig. 1.

The results of univariate and multivariate logistic regression analysis are shown in Table 4. A multivariate logistic regression analysis was performed for in hospital mortality based on the following variables: M-ATRIA-RS, troponin I level, history of coronary artery disease, COPD, malignancy and AF, serum levels of LDH, CRP, and ferritin levels. Among these variables, the M-ATRIA-RS, troponin I, LDH, and history of malignancy were identified as the independent predictors of in-hospital mortality. As they contained similar variables with the M-ATRIA, the CCI, ATRIA, CHA2DS2-VASc, mCHA2DS2-VASc, and CHADS scores were not included in this model. The predictive ability of our model was evaluated using the C statistics and showed a good discriminative capacity in predicting in-hospital mortality (C statistics=0.86, 95% CI: 0.82−0.90). The calibrations of both our model and M-ATRIA-RS to predict mortality were accurate in our study ($p = 0.14$ and $p = 0.82$, respectively).

The ROC analysis results showing the predictive accuracy of M-ATRIA-RS, ATRIA-RS, mCHA2DS2-VASc-RS, CHA2DS2-VASc-RS, CHADS2-RS, and CCI for in-hospital mortality are shown in Fig. 2. Based on a 95% CI, the areas under the curve (AUC) for M-ATRIA-RS, ATRIA-RS, mCHA2DS2-VASc-RS, CHA2DS2-VASc-RS, CHADS-RS, and CCI were 0.74, 0.72, 0.72, 0.68, 67, and 0.71, respectively ($p<0.001$, for all). A pairwise comparison of the ROC curves revealed that the predictive value of M-ATRIA-RS for in-hospital mortality was superior to the ATRIA-RS, mCHA2DS2-VASc-RS, CHA2DS2-VASc-RS, and CHADS-RS, but similar to that of the CCI (AUC$_{\text{M-ATRIA}}$ vs. AUC$_{\text{ATRIA}}$ Z-test=3.14, $p = 0.002$; AUC$_{\text{M-ATRIA}}$ vs. AUC$_{\text{mCHA2DS2-VASc}}$ Z-test=2.14, $p = 0.03$; AUC$_{\text{M-ATRIA}}$ vs. AUC$_{\text{CHA2DS2-VASc}}$ Z-test=4.23, $p<0.001$; AUC$_{\text{M-ATRIA}}$ vs. AUC$_{\text{CHADS}}$ Z-test=4.15, $p<0.001$; and AUC$_{\text{M-ATRIA}}$ vs. AUC$_{\text{CCI}}$ Z-test=1.46, $p = 0.14$).

DISCUSSION

The COVID-19 is a new strain which was not previously described in humans. After its first identification in Wuhan, Hubei province of China in December 2019, it

Table 2. Demographic and clinical characteristics of the patients according to M-ATRIA score.

Variable	M-ATRIA 0–1 (n = 448)	M-ATRIA 2–4 (n = 268)	M-ATRIA ≥5 (n = 285)	*P* value	*Post-hoc* analysis
Age (years)	48.5 (39−56)	60 (53−65)	76 (69−83)	<0.001	Group1vs2 *p*<0.001 Group1vs3 *p*<0.001 Group2vs3 *p*<0.001
Male sex	231 (51.6%)	156 (58.2%)	167 (64.4%)	0.1	
DM	24 (5.4%)	130(48.5%)	137 (48.1%)	<0.001	
Hypertension	38 (8.5%)	151 (56.3%)	214 (75.1%)	<0.001	
Hypercholesterolemia	27 (6%)	68 (25.4%)	68 (23.9%)	<0.001	
Previous CAD	16 (3.6%)	53 (19.8%)	91 (31.9%)	<0.001	
Previous CVD	10 (2.2%)	8 (3%)	19 (6.7%)	0.006	
COPD	40 (8.9%)	44 (16.4%)	48 (16.8%)	0.002	
Heart failure	1 (0.2%)	10 (3.7%)	36 (12.7%)	<0.001	
CKD	3 (0.7%)	18 (6.7%)	43 (15.1%)	<0.001	
AF	6 (1.3%)	12 (4.5%)	23 (8.1%)	<0.001	
Previous malignancy	8 (1.8%)	11 (4.1%)	7 (2.5%)	0.16	
Proteinuria	11 (2.5%)	30 (10.2%)	70(24.6%)	<0.001	
Length of hospital stay (days)	7 (4−12)	8 (5−12)	9 (5−14)	<0.001*	Group1vs2 p 0.005 Group1vs3 *p*<0.001 Group2vs3 p 0.99
ATRIA-RS	0 (0−1)	3 (1−3)	6 (5−8)	<0.001*	Group1vs2p< 0.001 Group1vs3 *p*<0.001 Group2vs3 *p*<0.001
CHADS-VASc-RS	1 (0−1)	2 (1−3)	4 (3−5)	<0.001*	Group1vs2 *p*<0.001 Group1vs3 *p*<0.001 Group2vs3 *p*<0.001
mCHADS-VASc-RS	1 (0−1)	2 (2−3)	4 (3−5)	<0.001*	Group1vs2 *p*<0.001 Group1vs3 *p*<0.001 Group2vs3 *p*<0.001
CHADS-RS	0	1 (0−2)	2 (1−3)	<0.001*	Group1vs2 *p*<0.001 Group1vs3 *p*<0.001 Group2vs3 *p*<0.001
CCI	1 (0−2)	2(2−4)	4 (3−6)	<0.001*	Group1vs2 *p*<0.001 Group1vs3 *p*<0.001 Group2vs3p< 0.001
In-hospital mortality	29 (6.5%)	41 (15.3%)	98 (34.4%)	<0.001	
ICU admission	74 (16.5%)	81 (30.3%)	129 (45.3%)	<0.001	
Mechanical ventilation	64 (14.3%)	67 (25.3%)	116 (40.7%)	<0.001	
In-hospital medications					
Hydroxychloroquine	323 (72.3%)	196 (73.7%)	189 (66.8%)	0.16	
Oseltamivir	199 (44.6%)	139 (52.5%)	145 (51.2%)	0.08	
Favipiravir	120 (26.8%)	93 (35%)	117 (41.3%)	<0.001	
Azithromycin	370 (82.8%)	235 (87.7%)	245 (86.3%)	0.16	
Lopinavir/Ritonavir	133 (29.8%)	76 (28.6%)	114 (40.3%)	0.004	
Remdesivir	1 (0.2%)	5 (1.9%)	3 (1.1%)	0.07	

Data are given in median (interquartile range) or number and frequency, unless otherwise stated. DM: diabetes mellitus; CAD: coronary artery disease; CVD: cerebrovascular disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; AF: atrial fibrillation; ATRIA-RS: Anticoagulation and Risk Factors in Atrial Fibrillation Risk Score; M-ATRIA-RS: modified Anticoagulation and Risk Factors in Atrial Fibrillation Risk Score; CCI: Charlson Comorbidity Index; ICU: intensive care unit.

became a global pandemic.[1] However, there is still a lack of well-validated scoring systems for risk prediction in COVID-19. The ATRIA scoring system is a simple and effective tool for easy risk stratification in different entities.[16,17]

In the present study, we investigated whether M-ATRIA-RS was an independent predictor of mortality in patients hospitalized for COVID-19 and compared its discrimination capability with CHADS, CHA2DS2-VASc, and mCHA2DS2-VASc-RS. Our study results showed that higher M-ATRIA scores were associated with worse outcomes in patients with COVID-19. Also, the M-ATRIA scores had a good discriminative ability to predict in-hospital mortality in hospitalized COVID-19 patients. Additionally, the M-ATRIA-RS was found to be superior to the ATRIA, CHADS, CHA2DS2-VASc, and mCHA2DS2-VASc scoring systems, but similar to the CCI in terms of predicting mortality. This scoring system

Table 3. Laboratory data of the patients according to M-ATRIA score.

Variable	M-ATRIA 0–1 (n = 448)	M-ATRIA 2–4 (n = 268)	M-ATRIA ≥5 (n = 285)	P value	Post-hoc analysis
Troponin I (ng/dL)	6 (3–20)	12.8 (4.1–86.8)	30 (10.1–130)	<0.001*	Group1vs2 $p<0.001$ Group1vs3 $p<0.001$ Group2vs3 0.66
CK-MB (ug/L)	10 (5.9–15.3)	12 (7–28.8)	21 (11–39)	<0.001*	Group1vs2 p 0.01 Group1vs3 $p<0.001$ Group2vs3 $p<0.001$
D-dimer (ug/L)	520 (170–1678)	931 (336–2858)	1000 (146–2740)	0.002*	Group1vs2 p 0.37 Group1vs3 $p<0.001$ Group2vs3 p 0.19
White blood cell (/mm^3)	5960 (4380–8260)	6520 (4735–9620)	6800 (4800–9600)	0.001*	Group1vs2 p 0.1 Group1vs3 p 0.001 Group2vs3 p 0.55
Neutrophil (/mm^3)	4900 (3250–7600)	4500 (3000–6680)	3600 (2400–5800)	<0.001*	Group1vs2 p 0.16 Group1vs3 $p<0.001$ Group2vs3 p 0.002
Lymphocyte (/mm^3)	1000 (620–1550)	935 (590–1480)	800 (450–1160)	<0.001*	Group1vs2 p 0.39 Group1vs3 $p<0.001$ Group2vs3 $p<0.001$
Hemoglobin (g/dL)	13.1 (12.–14.4)	13 (11.2–13.9)	12.8 (11–14.2)	<0.001*	Group1vs2 p 0.09 Group1vs3 $p<0.001$ Group2vs3 p 0.41
Platelet (10^3/mm^3)	204 (167–275)	207 (149–285)	183 (141–268)	0.03	Group1vs2 p 0.99 Group1vs3 p 0.03 Group2vs3 p 0.21
Urea (mg/dL)	25 (20–36.5)	39 (29–59)	53 (38–89)	<0.001*	Group1vs2 $p<0.001$ Group1vs3 $p<0.001$ Group2vs3 $p<0.001$
Creatinine (mg/dL)	0.8 (0.7–0.98)	0.9 (0.77–1.18)	1.1 (0.86–1.8)	<0.001*	Group1vs2 $p<0.001$ Group1vs3 $p<0.001$ Group2vs3 $p<0.001$
AST (U/L)	32.5 (22–50.8)	41 (24.3–55.8)	31 (23–54)	0.001*	Group1vs2 p 0.16 Group1vs3 p 0.001 Group2vs3 p 0.42
ALT (U/L)	28 (18–45)	27.5 (21–50.5)	20 (13–29)	0.003*	Group1vs2 p 0.99 Group1vs3 p 0.01 Group2vs3 p 0.005
Glucose (mg/dL)	106 (92–134)	116 (100–237)	138 (104–178)	<0.001*	Group1vs2 $p<0.001$ Group1vs3 $p<0.001$ Group2vs3 p 0.66
LDH (U/L)	343 (239–484)	362 (262–507)	377 (281–523)	<0.001*	Group1vs2 p 0.09 Group1vs3 $p<0.001$ Group2vs3 p 0.18
Ferritin (ug/L)	306 (100–814)	445 (183–1303)	529 (175–1306)	0.004*	Group1vs2 p 0.04 Group1vs3 p 0.007 Group2vs3 p 0.99
CRP (mg/L)	16 (6–53)	18 (8–76)	30 (12–119)	<0.001*	Group1vs2 $p<0.001$ Group1vs3 $p<0.001$ Group2vs3 p 0.19
Procalcitonin (ug/L)	0.1 (0.05–0.55)	0.18 (0.05–1.02)	0.55 (0.11–1.8)	<0.001*	Group1vs2 p 0.001 Group1vs3 $p<0.001$ Group2vs3 p 0.03
Albumin (mg/dL)	3.7 (3.3–4)	3.4 (2.9–3.9)	3.4 (2.9–3.8)	<0.001*	Group1vs2 $p<0.001$ Group1vs3 $p<0.001$ Group2vs3 p 0.99

Data are given in median (interquartile range), unless otherwise stated.
* Kruskal-Wallis test.ATRIA-RS: Anticoagulation and Risk Factors in Atrial Fibrillation Risk Score; CK-MB: creatine kinase-myocardial band; AST: aspartate transaminase; ALT: alanine transaminase; LDH: lactate dehydrogenase; CRP: C-reactive protein.
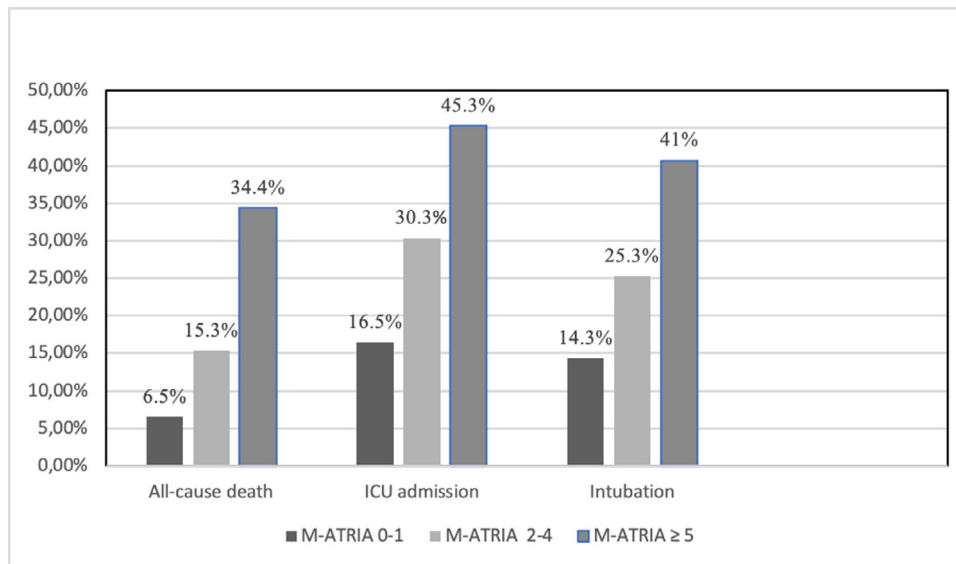
FIG. 1. The rates of in-hospital mortality, ICU admission, and requirement for invasive mechanical ventilation of the groups. M-ATRIA-RS: modified Anticoagulation and Risk Factors in Atrial Fibrillation Risk Score; ICU: intensive care unit.

Table 4. Univariate and multivariaate analysis of possible predictors of in hospital mortality.

	Univariate		Multivariate	
	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
M-ATRIA-RS	1.39 (1.3−1.48)	<0.001	1.26 (1.14−1.40)	<0.001
ATRIA-RS	1.32 (1.25−1.41)	<0.001		
mCHADS-VASc-RS	1.58 (1.43−1.75)	<0.001		
CHADS-VASc-RS	1.44 (1.31−1.59)	<0.001		
CHADS-RS	1.70 (1.48−1.95)	<0.001		
CCI	1.39 (1.29−1.51)	<0.001		
Troponin I	1.001 (1.001−1.003)	<0.001	1.001 (1.000−1.001)	<0.001
Male sex	1.47 (1.04−2.07)	0.03		
Age	1.05 (1.04−1.07)	<0.001		
Hypertension	2.22(1.58−3.10)	<0.001		
DM	1.69 (1.19 −2.39)	0.003		
CAD	2.89 (1.97−4.25)	<0.001	1.53 (0.78−2.97)	0.21
Heart failure	7.82 (4.27−14.33)	<0.001		
CVD	1.63 (0.75−3.51)	0.22		
CKD	3.32 (1.95−5.69)	<0.001		
Proteinuria	5.61 (3.69−8.55)	<0.001		
Atrial fibrillation	2.41 (1.22−4.76)	<0.001	0.93 (0.30−2.84)	0.89
COPD	2.1 (1.37−3.20)	0.001	1.12 (0.56−2.23)	0.76
Previous malignancy	5.29 (2.41−11.63)	<0.001	3.91 (1.33−11.5)	0.01
D-dimer	1.001 (1.001−1.002)	<0.001		
LDH	1.003 (1.002−1.004)	<0.001	1.002 (1.001−1.004)	0.001
CRP	1.007 (1.005−1.009)	<0.001	1.002 (0.99−1.006)	0.15
Procalcitonin	1.19 (1.12−1.26)	<0.001		
Ferritin	1.001 (1.000−1.002)	<0.001	1.001 (1.000−1.001)	0.07

ATRIA-RS: Anticoagulation and Risk Factors in Atrial Fibrillation Risk Score; M-ATRIA-RS: modified Anticoagulation and Risk Factors in Atrial Fibrillation Risk Score; CCI: Charlson Comorbidity Index; CI: confidence interval; DM: diabetes mellitus; CAD: coronary artery disease; CVD: cerebrovascular disease; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease; LDH: lactate dehydrogenase; CRP: C-reactive protein.
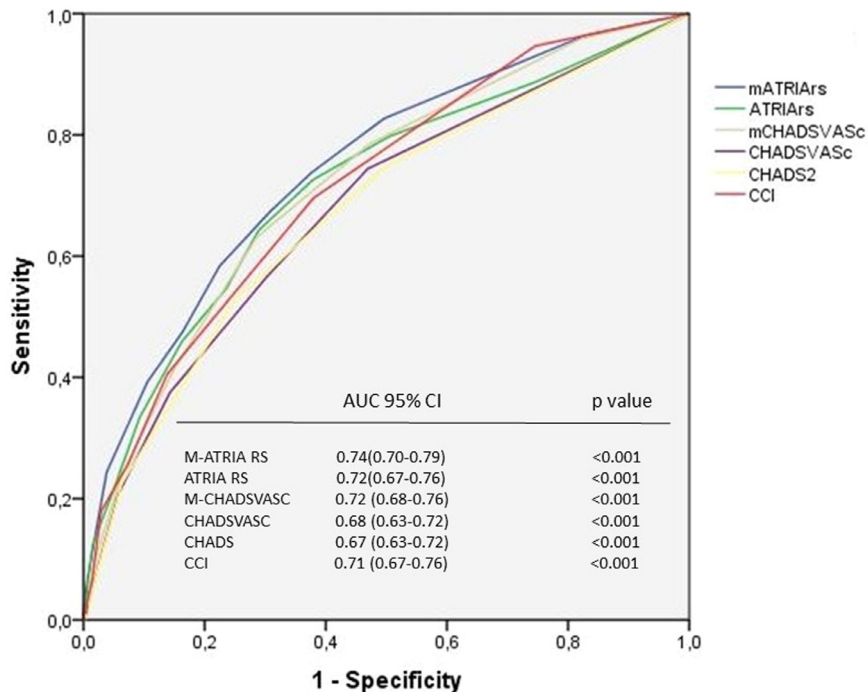
FIG. 2. ROC analysis results showing the predictive accuracy of M-ATRIA-RS, ATRIA-RS, mCHA2DS2-VASc-RS, CHA2DS2-VASc-RS, CHADS2-RS, and CCI for in-hospital mortality. ATRIA-RS: Anticoagulation and Risk Factors in Atrial Fibrillation Risk Score; M-ATRIA-RS: modified Anticoagulation and Risk Factors in Atrial Fibrillation Risk Score; ROC: receiver operating characteristics. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

was also an independent predictor of in-hospital mortality in COVID-19 patients.

Consistent with recent studies investigating the prognostic risk factors for COVID-19, our study showed that male sex and age were strongly associated with an increased risk of in-hospital mortality. Based on this finding, we can speculate that the discriminative performance of the M-ATRIA-RS is significantly improved by simply changing its sex component from female to male. Advanced age is one of the major risk factors which is strongly associated with severe COVID-19 and mortality.[18] COVID-19 infection has been shown to be more severe in older patients, resulting in a high rate of mortality. Of note, elderly patients with COVID-19 are more likely to progress to severe disease requiring ICU admission.[19] In a study including 138 hospitalized patients with COVID-19 pneumonia, the median age of the ICU patients was 66 years *versus* 51 years among those not receiving ICU care.[20] In another study conducted in the United States, the case-fatality rate (CFR) for COVID-19 was found to be 10 to 27% in patients aged above 85 years.[21] In the Italian National Institute of Health report, the overall CFR was found to be <1% in the age group of <50 years with a rapid increase in the age group of ≥60 years (16.9% and 24.4% in the age groups of 70 to 79 years and ≥80 years, respectively).[22] According to the Korea Disease Control and Prevention Agency, the overall CFR was 2.37% in 11,344 patients with confirmed cases; however, it was much higher in the elderly (10.9%

in patients aged 70 to 79 years and 26.6% in patients aged ≥80 years).[23] In another analysis of 44,672 cases in China, the overall CFR was 2.3%; however, the CFR was 8.0% in patients aged 70 to 79 years and 14.8% in patients aged ≥80 years.[24] However, there is age-based exponential increase in the fatality rate, regardless of the geographic region. Unlike CHA2DS2-VASc and CHADS scores, a more detailed classification was performed for age in the ATRIA-RS and the points given to age was higher than the other components. Bringing the age criterion forefront, which is the leading criteria, may explain the fact that M-ATRIA-RS is an independent predictor of in-hospital mortality in our study.

Elderly individuals and those having a higher prevalence of comorbidities have been shown to be more susceptible to SARS-CoV-2. The majority of the patients have at least one comorbidity in severe groups, and cardiovascular disease, cerebrovascular disease, chronic kidney disease, hypertension, and diabetes are the most common comorbidities in this population.[25] Although CCI includes a higher number of risk factors compared to ATRIA-RS (*i.e.*, malignancy, liver disease, and rheumatic disease), our study found that CCI and M-ATRIA-RS had a similar ability to predict mortality in COVID-19 patients. This can be attributed to the fact that many individual risk factors included in the M-ATRIA-RS are also the factors related to COVID-19 morbidity and mortality. However, further large-scale, prospective studies are needed to confirm this concept.

Furthermore, in a study including COVID-19 patients, early LDH levels were found to be a good predictor of lung injury and severity of COVID-19 in the course of the disease.[26] There was also a correlation between higher LDH levels and worse clinical outcomes in previous studies.[27,28] Abnormal LDH levels may be due to decreased oxygenation and upregulation of the glycolytic pathway, as well as multiple organ injuries. Similarly, our study demonstrated that higher LDH levels were associated with worse outcomes. Myocardial injury is frequent in patients with COVID-19, showing an association with the severity of infection. Although it varies between COVID-19 studies, myocardial injury is usually defined as the elevation of high-sensitivity cardiac troponin (hs-cTn) above the 99th percentile of its upper limit of normal.[29] Increased levels of hs-cTn are associated with the severity of the disease and mortality rate in COVID-19.[29,30] In our study, elevated LDH and troponin levels were independently associated with in-hospital mortality in COVID-19 patients. In addition, patients with malignancies were found to have a higher risk of mechanical ventilation in the ICU or COVID-19-related mortality.[31] Consistent with this finding, malignancy was also one of the independent predictors of mortality in our study.

Nonetheless, this study has some limitations. First, the retrospective nature of the study precludes the generalization of the results to the overall population. Second, COVID-19 may manifest with a diverse clinical spectrum in every patient, particularly in different ethnic groups and the retrospective design may have limited the quality of data collected. Third, the missing data for all prognostic variables were assumed to be normal in this study, which may have affected the prognostic value of the scores, particularly of the CCI. Therefore, further large-scale, prospective studies are warranted to confirm the relationship between the M-ATRIA scores and poor outcomes in patients with COVID-19.

CONCLUSIONS

In conclusion, our study results suggest that M-ATRIA-RS is a useful tool to predict in-hospital mortality among hospitalized patients with COVID-19. It also shows superiority over the mCHA2DS2-VASc-RS in predicting mortality in this patient group and is more easily calculable than the CCI score. Based on these findings, it seems to be a simplified means of rapid risk assessment at the time of hospital admission, contributing to identification of identify high-risk patients and early treatment and close follow-up with recommendations to the family and/or relatives of the patient.

DECLARATIONS

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval

This study was approved by the Istanbul Medeniyet University and Goztepe Prof. Dr. Suleyman Yalcin City Ethics Committee Ethics Committee with the Approval No:2020/0654

DECLARATION OF COMPETING INTEREST

The authors declare they have no potential conflict of interest regarding the investigation, authorship, and/or publication of this article.

REFERENCES

1. The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) — China, 2020[J]. China CDC Weekly. 2020;2(8):113−122.
2. **Guan WJ, Ni YZ, Hu Y, Liang HW, Ou QC, He XJ, et al.** Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708−1720.
3. **Luis F.** García immune response, inflammation, and the clinical spectrum of COVID-19. *Front Immunol*. 2020 Jun 16;11:1441.
4. **Shahid Z, Kalayanamitra R, McClafferty B, et al.** COVID-19 and older adults: what we know. *J Am Geriatr Soc*. 2020 May;68(5):926−929.
5. **Chen R, Liang W, Jiang M, et al.** Medical Treatment Expert Group for COVID-19. Risk factors of fatal outcome in hospitalized subjects with coronavirus disease 2019 from a nationwide analysis in China. *Chest*. 2020 Jul;158(1):97−105.
6. **Wynants L, Calster B V, Collins G S, et al.** Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. *BMJ*. 2020 Apr;7(369):m1328.
7. **Kirchhof P, Benussi S, Kotecha D, et al.** 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893−2962.
8. **Singer DE, Chang Y, Borowsky LH, 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;21:(3) e000250. Jun.
9. **Wang T, Chen R, Liu C, et al.** Attention should be paid to venous thromboembolism prophylaxis in the management of COVID19. *Lancet Haematol*. 2020;7(5):e362−e363.
10. **Cetinkal G, Kocas BB, Ser OS, et al.** Assessment of the Modified CHA2DS2VASc Risk score in predicting mortality in patients hospitalized with COVID-19. *Am J Cardiol*. 2020 Nov 15;135:143−149.
11. **Quisi A, Alıcı G.** Hr Harbalıoglu H, The CHA2DS2-VASc score and in-hospital mortality in patients with COVID-19: a multicenter retrospective cohort study. *Turk Kardiyol Dern Ars*. 2020;48(7):656−663.
12. **van den Ham HA, Klungel OH, Singer DE, et al.** 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;66:1851−1859.
13. **Aspberg S, Chang Y, Atterman A, et al.** 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;37:3203−3210.
14. **Levey AS, Bosch JP, Lewis JB, et al.** A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461−470.
15. **Charlson ME, Pompei P, Ales KL, MacKenzie CR.** A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373−383.

16. **Aksoy F, Bagcı A.** Predictive value of ATRIA risk score for contrast-induced nephropathy after percutaneous coronary intervention for ST-segment elevation myocardial infarction. *Rev Assoc Med Bras (1992)*. 2019 Nov;65(11):1384–1390.

17. **Cetinkal G, Kocas C, Kocas BB, et al.** Comparative performance of AnTicoagulation and risk factors in atrial fibrillation and global registry of acute coronary events risk scores in predicting long-term adverse events in patients with acute myocardial infarction. *Anatol J Cardiol*. 2018;20:77–84. 78.

18. **Shaw AC, Goldstein RD, Montgomery RR.** Age-dependent dysregulation of innate immunity. *Nat. Rev Immunol.*. 2013;13:875–887.

19. **Kang SJ, Jung SI.** Age-related morbidity and mortality among patients with COVID-19. *Infect Chemother*. 2020 Jun; 52:(2):154–164.

20. **Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al.** Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061–1069.

21. **CDC.** COVID-19 Response Team Severe outcomes among patients with coronavirus disease 2019 (covid-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:343–346.

22. Istituto Superiore di Sanità. Epidemia COVID-19. Available at: https://www.iss.it/documents/20126/0/Bollettino+sorveglianza+integrata+COVID-19_19+marzo+2020.pdf/e56791f7-820c-555e-8b0c-750c9db2883d?t=1584724596303. Accessed May 10, 2020.

23. Korea Centers for Disease Control and Prevention (KCDC). Status of COVID-19 in Korea. Available at: http://ncov.mohw.go.kr/bdBoardList_Real.do?brdId=1&brdGubun=11&ncvContSeq=&contSeq=&board_id=&gubun=. Accessed May 29, 2020.

24. The novel coronavirus pneumonia emergency response epidemiology team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) - China, 2020. *China CDC Weekly*. 2020;2:113–122.

25. **Barek A, Aziz A, Islam MS.** Impact of age, sex, comorbidities and clinical symptoms on the severity of COVID-19 cases: a meta-analysis with 55 studies and 10014 cases. *Heliyon*. 2020 Dec;6(12):05684.

26. **Han Y, Zhang H, Mu S, et al.** Lactate dehydrogenase, a risk factor of severe COVID-19 patients. *Aging (Albany NY)*. 2020 Jun 24;12(12):11245–11258.

27. **Henry BM, Aggarwal G, Wong J, et al.** Lactate dehydrogenase levels predict coronavirus disease 2019 (COVID-19) severity and mortality: a pooled analysis. *Am J Emerg Med*. 2020;38(9):1722–1726. 2020 Sep; 38.

28. **Zhou F, Yu T, Du R, et al.** Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*. 2020;395. 1054−.

29. **Guo T, Fan Y, Chen M, et al.** Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020 Jul 1;5(7):811–818.

30. **Shi S, Qin M, Shen B, et al.** Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020 Jul 1;5(7):802–810.

31. **Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al.** Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335–337.