Prognostic Accuracy of the Modified CHA_2DS_2-VASc Score in COVID-19 Patients Admitted to the Emergency Department Due to Clinical Worsening

Performance Prognóstica do Score CHA_2DS_2-VASc Modificado em Doentes com COVID-19 Admitidos no Serviço de Urgência em Contexto de Agravamento Clínico

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ABSTRACT

Introduction: Risk factors comprising the CHA_2DS_2VASc score are recognized as risk factors for venous thromboembolism and mortality in COVID-19 patients. A modified CHA_2DS_2VASc score (M-CHA_2D_2VASc), developed by changing gender criteria from female to male, has been proposed to predict in-hospital mortality in COVID-19 patients. The aim of this study was to evaluate the prognostic accuracy of M-CHA_2D_2VASc for adverse clinical outcomes and short-term mortality in COVID-19 patients admitted to the Emergency Department.

Material and Methods: Retrospective study of patients admitted to the ED who underwent computed tomography pulmonary angiography due to suspected pulmonary embolism or clinical worsening. Patients were stratified into three M-CHA_2DS_2-VASc risk-categories: low (0 - 1 points), intermediate (2 - 3 points) and high-risk (≥ 4 points).

Results: We included 300 patients (median age 71 years, 59% male). The overall mortality was 27%. The M-CHA_2DS_2-VASc score was higher in non-survivors compared to survivors [4 (IQR:3 - 5) *vs* 2 (IQR: 1 - 4), respectively, $p < 0.001$). The M-CHA_2DS_2-VASc score was identified as an independent predictor of mortality in a multivariable logistic regression model (OR 1.406, $p = 0.007$). The Kaplan-Meier survival curves showed that the M-CHA_2DS_2-VASc score was associated with short-term mortality (log-rank test < 0.001), regardless of hospitalization (log-rank test $p < 0.001$ and $p = 0.007$, respectively). The survival proportion was 92%, 80% and 63% in the lower, intermediate, and higher risk-groups. As for the risk-categories, no difference was found in pulmonary embolism, Intensive Care Unit admission, and invasive mechanical ventilation.

Conclusion: The M-CHA_2DS_2-VASC score might be useful for prompt risk-stratification in COVID-19 patients during admission to the Emergency Department.

Keywords: COVID-19; Mortality; Risk Assessment; SARS-CoV-2

RESUMO

Introdução: O *score* CHA_2DS_2VASc engloba variáveis reconhecidas como fatores de risco para tromboembolismo venoso e mortalidade nos doentes com COVID-19. O *score* CHA_2DS_2VASc modificado (M-CHA_2DS_2-VASc), criado pela alteração do critério de género de feminino para masculino, foi proposto como preditor da mortalidade intra-hospitalar nestes doentes. O objetivo deste trabalho foi avaliar o valor prognóstico do M-CHA_2DS_2-VASc como preditor de eventos adversos e mortalidade a curto-prazo nos doentes com COVID-19 admitidos no Serviço de Urgência.

Material e Métodos: Análise retrospetiva de doentes admitidos no Serviço de Urgência que realizaram tomografia computorizada pulmonar com administração de contraste por agravamento clínico e/ou suspeita de embolia pulmonar. Definiram-se três categorias de risco M-CHA_2DS_2-VASc: baixo, intermédio e alto (0 - 1; 2 - 3 e ≥ 4 pontos, respectivamente).

Resultados: Incluíram-se 300 doentes (idade mediana: 71 anos, 59% homens). A mortalidade global foi 27%. O M-CHA_2DS_2-VASc foi maior em não sobreviventes [4 (IQR: 3 - 5) *vs* 2 (IQR: 1 - 4), $p < 0,001$) e constituiu um preditor independente de mortalidade numa análise multiparamétrica (OR: 1.406, $p = 0,007$). As curvas de sobrevivência demonstraram a associação do M-CHA_2DS_2-VASc com a mortalidade a curto-prazo (*log-rank test* < 0,001), independentemente dos doentes serem hospitalizados ou não (*log-rank test* $p <$ 0,001 e $p = 0,007$, respetivamente). A taxa de sobrevida foi de 92%, 80% e 63% nos grupos de baixo, intermédio e alto risco. De acordo com as categorias de risco, não foram encontradas diferenças na incidência de embolia pulmonar, admissão em Cuidados Intensivos e ventilação mecânica invasiva.

Conclusão: O M-CHA_2DS_2-VASc pode ser útil para estratificação de risco nos doentes com COVID-19 admitidos no Serviço de Urgência.

Palavras-chave: Avaliação de Risco; COVID-19; Mortalidade; SARS-CoV-2

INTRODUCTION

The novel coronavirus, known as SARS-CoV-2, emerged at the end of 2019 in Wuhan, China, and became a major public health emergency worldwide.[1] Since the initial reports, SARS-CoV-2 infection has been associated with increased arterial and venous thromboembolic events, mainly pulmonary embolism (PE).[2–4]

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The CHA_2DS_2-VASc score is a well-validated and widely used score to determine thromboembolic risk and guide anticoagulation in patients with non-valvular atrial fibrillation.[5] Moreover, its prognostic value has been demonstrated as an independent predictor of mortality in several cardiovascular diseases.[6–8]

Several individual risk factors comprising the CHA_2DS_2-VASc score are also recognized as risk factors for mortality in COVID-19 patients. However, the female gender is an exception to this pattern.[9–11] Therefore, a recent study proposed a modified CHA_2DS_2-VASc score (M-CHA_2DS_2-VASc) as an independent predictor of in-hospital mortality in hospitalized COVID-19 patients.[12] This new proposed score was created by changing gender criteria from female to male, considering that the male gender was associated with increased thromboembolic events and mortality in COVID-19 patients.[13,14] However, it remains unclear whether the score has discriminative power to predict short-term mortality, namely when applied to patients admitted in the Emergency Department (ED), and whether hospitalization is required or not.

The purpose of this study was to investigate whether the M-CHA_2DS_2-VASc score is an independent predictor of PE occurrence, admission to the intensive care unit (ICU) and invasive mechanical ventilation, and to validate it as an independent predictor of short-term mortality in COVID-19 patients admitted to the ED due to clinical worsening.

MATERIAL AND METHODS

Retrospective single-centre study performed in a tertiary care university hospital (Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal) from the 1st April 2020 to the 31st January 2021. The study was performed in accordance with the 2013 Helsinki Declaration and was approved by the Ethics Committee of our institution. Since the study involved completely anonymized data extraction from electronic medical records, patient consent was not required.

We selected consecutive adult patients with confirmed SARS-CoV-2 infection admitted to the ED who underwent computed tomography pulmonary angiography (CTPA) due to clinical worsening and/or PE suspicion. The SARS-CoV-2 infection diagnosis was established by a positive result on the real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swabs or, in patients with prior diagnosis, by consulting the national registration platform of COVID-19 patients (TRACE-COVID).

Data on epidemiological, demographic, clinical, laboratory and adverse clinical outcomes were collected from electronic medical records. Laboratory results included were obtained within 24 hours from the time of ED admission. The laboratory test was a quantitative assay with a 500 ng/mL threshold for D-dimer and 300 pg/mL for N-terminal prohormone BNP (NT-proBNP). Myocardial injury was defined as elevated high-sensitive Troponin T (cTnT-hs) values with at least one value above the 99th percentile upper reference limit.

All patients were followed up until 11th March 2021 or death, whichever came first.

The primary objective was to investigate the prognostic value of the M-CHA_2DS_2-VASc score as an independent predictor of adverse clinical outcomes and short-term mortality in COVID-19 patients admitted to the ED with clinical worsening. Adverse clinical outcomes were defined as PE occurrence, admission to the intensive care unit (ICU) and invasive mechanical ventilation.

The secondary objectives were to evaluate whether the M-CHA_2DS_2-VASc score predicted mortality in hospitalized patients and those discharged from ED, and to compare its prognostic value with the CHA_2DS_2-VASc score and cardiac biomarkers such as cTnT-hs and NT-proBNP.

M-CHA_2DS_2-VASc and CHA_2DS_2-VASc score risk-stratification

The CHA_2DS_2-VASc score was calculated based on the scoring system as follows: 2 points were assigned for age 75 and over and a history of stroke and/or transient ischemic attack, while 1 point was assigned for hypertension, diabetes, congestive heart failure, vascular disease (included peripheral artery disease, prior myocardial infarction, and evidence of aortic plaque), female sex, and age 65 to 74. The M-CHA_2DS_2-VASc risk score was calculated with the same items and scoring of CHA_2DS_2-VASc, except for the gender category in which 1 point was attributed to the male gender and 0 points to the female gender. The CHA_2DS_2-VASc and M-CHA_2DS_2-VASc scores were calculated by an investigator who was blinded to the patient-survival data.

For both M-CHA_2DS_2-VASc and CHA_2DS_2-VASc scores, patients were stratified into three terciles, corresponding to lower (0 - 1 points), intermediate (2 - 3 points)and high risk (≥ 4 points) of thromboembolic events.

Statistical analysis

Categorical variables were expressed as frequency counts and percentages, and continuous variables as median and interquartile range (IQR) or mean and standard deviation (SD) according to whether the distribution was normal or not. The Kolmogorov-Smirnov test was performed to test distributions for normality. The independent samples t-test or the Mann-Whitney U-test were used to compare continuous variables and the chi-squared test or Fisher's exact test were used to compare categorical variables, as appropriate based on distribution. The Kruskal-Wallis test for continuous variables and the chi-square for categorical variables were used to compare M-CHA_2DS_2-VASc risk groups. Independent predictors of PE and short-term mortality were determined by logistic regression analysis. Each independent variable's odds ratio (OR) and 95% confidence interval (CI) were calculated.

The discriminative power of CHA_2DS_2-VASc and M-CHA_2DS_2-VASc scores, cTnT-hs and NT-proBNP to predict mortality was calculated by differences in the area under the curve (AUC) according to the receiver-operating characteristics (ROC) curve. ROC curves were compared using the De-Long method. The Youden index was used for the de-

termination of the optimal cut-off point of M-CHA_2DS_2-VASc score. Kaplan-Meier survival analysis with Log-rank test, stratified by M-CHA_2DS_2-VASc risk categories, was used for the outcome time do death.

Statistical significance was defined as a *p* value < 0.05. The statistical software used to analyze the data was SPSS® v.26 (IBM).

RESULTS

This study included 300 patients with proven SARS-CoV-2 infection admitted to the ED between April 2020 and January 2021 and who underwent CTPA due to clinical worsening and/or PE suspicion.

The baseline characteristics of the cohort are described in Table 1. The median age was 71 (IQR 60 - 82) years, with 59% of the patients being male. The most prevalent comorbidity was hypertension (59%) followed by chronic kidney disease (33%), dyslipidemia (32%) and diabetes (28%). Both M-CHA_2DS_2-VASc and CHA_2DS_2-VASc scores medians were 3 (IQR 1 - 4).

The median follow-up time was 56 (IQR 40 - 107) days. Most patients were hospitalized (83%), and 49 patients (16%) were admitted to the ICU at a certain time-point of their clinical evolution. The overall mortality rate was 27% (n = 81). As for the patients that died, 84% (n = 68) had been hospitalized.

M-CHA_2DS_2-VASc and prediction of adverse clinical outcomes

Pulmonary embolism was diagnosed in 46 patients (15%), with a median age of 76 (IQR 65 - 84) years, being 48% males. The vascular allocation of emboli showed a predominantly central distribution (59%), affecting the main and lobar arteries (15% and 44%, respectively). Most PE

Table 1 – Baseline characteristics of COVID-19 patients (all patients) and according to the outcome (survivor or non-survivor)

Variable	All patients (n = 300)		Survivors (n = 219)		Non-survivors (n = 81)		*p* value*
Age, median (Q1 - Q3) (years)	71	(60 - 82)	69	(56 - 78)	81	(73 - 88)	***p* < 0.001**
Gender - Male, n (%)	176	(59.0%)	122	(56.0%)	54	(67.0%)	*p* = 0.113
Comorbidities							
Obesity, n (%)	52	(17.3%)	40	(18.3%)	12	(14.8%)	*p* = 0.607
Arterial hypertension, n (%)	177	(59.0%)	121	(55.3%)	56	(69.1%)	***p* = 0.034**
Dyslipidemia, n (%)	95	(31.7%)	74	(33.8%)	21	(25.9%)	*p* = 0.211
Diabetes mellitus, n (%)	83	(27.7%)	58	(26.5%)	25	(30.9%)	*p* = 0.469
Chronic heart failure, n (%)	25	(8.3%)	16	(7.3%)	9	(11.1%)	*p* = 0.346
Ischemic heart disease, n (%)	27	(9.0%)	18	(8.2%)	9	(11.1%)	*p* = 0.496
Atrial fibrillation, n (%)	27	(9.0%)	16	(7.3%)	11	(13.6%)	*p* = 0.111
Chronic kidney disease, n (%)	100	(33.3%)	63	(28.8%)	37	(45.7%)	***p* = 0.008**
Chronic obstructive pulmonary disease, n (%)	43	(14.3%)	31	(14.2%)	12	(14.8%)	*p* = 0.855
Sleep apnea, n (%)	17	(5.7%)	12	(5.5%)	5	(6.2%)	*p* = 0.784
History of smoking, n (%)	38	(12.7%)	22	(10.1%)	16	(19.8%)	***p* = 0.044**
Cerebrovascular disease, n (%)	27	(9.0%)	14	(6.4%)	13	(16.0%)	***p* = 0.021**
Scores							
M-CHADSVASC, median (Q1 - Q3) (points)	3	(1 - 4)	2	(1-4)	4	(3 - 5)	***p* < 0.001**
CHADSVASC, median (Q1 - Q3) (points)	3	(1 - 4)	2	(1-4)	4	(2 - 5)	***p* < 0.001**
Laboratory results							
D-dimer, median (Q1 - Q3) (ng/mL)	1.50	(0.84 - 4.01)	1.26	(0.77 - 2.65)	2.68	(1.20 - 12.63)	***p* < 0.001**
cTnT-hs, median (Q1 - Q3) (ng/L)	18	(9 - 37)	13	(8 - 27)	35	(19 - 64)	***p* < 0.001**
NT-proBNP, median (Q1 - Q3) (pg/mL)	462	(121 - 1559)	302	(74 - 783)	1133	(436 - 2651)	***p* < 0.001**
Creatinine, median (Q1 - Q3) (mg/dl)	0.97	(0.67 - 1.24)	0.96	(0.80 - 1.20)	1.06	(0.85 - 1.55)	***p* = 0.038**
eGFR, median (Q1 - Q3) (mL/min/1.73 m^2)	73	(50 - 89)	75	(54 - 91)	62	(40 - 81)	***p* < 0.001**
Clinical outcomes							
Pulmonary embolism, n (%)	46	(15.3%)	31	(14.2%)	15	(16.0%)	*p* = 0.369
Hospitalization, n (%)	249	(83.0%)	181	(82.6%)	68	(84.0%)	*p* = 0.864
ICU admission, n (%)	49	(16.3%)	27	(12.3%)	22	(27.2%)	***p* = 0.002**
Invasive mechanical ventilation, n (%)	36	(12.0%)	16	(7.3%)	20	(24.7%)	***p* < 0.001**

* Referring to the difference between survivors and non-survivors.
cTnT-hs: high-sensitive Troponin T; NT-proBNP: N-terminal prohormone BNP; eGFR: estimated glomerular filtration rate; ICU: intensive care unit

Table 2 – Baseline characteristic patients according to M-CHA_2DS_2-VASc score stratification

Variable	M-CHADSVASc 0 - 1 (n = 76)		M-CHADSVASc 2 - 3 (n = 118)		M-CHA_2DS_2-VASc ≥ 4 (n = 106)		*p* value	Post-hoc analysis
Age, median (Q1 - Q3) (years)	56	(43 - 61)	71	(65 - 82)	80	(75 - 86)	$p < 0.001$	Group 1 *vs* 2: $p < 0.001$ Group 1 *vs* 3: $p < 0.001$ Group 2 *vs* 3: $p < 0.001$
Gender - Male, n (%)	36	(47.4%)	62	(52.5%)	78	(73.6%)	$p < 0.001$	
Comorbidities								
Obesity, n (%)	19	(25.0%)	21	(17.8%)	12	(11.3%)	$p = 0.055$	
Arterial hypertension, n (%)	11	(14.5%)	67	(56.8%)	99	(93.4%)	$p = 0.012$	
Dyslipidemia, n (%)	14	(18.4%)	40	(33.9%)	41	(38.7%)	$p < 0.001$	
Diabetes mellitus, n (%)	1	(1.3%)	23	(19.5%)	59	(55.7%)	$p < 0.001$	
Chronic heart failure, n (%)	0	(0.0%)	5	(4.2%)	20	(18.6%)	$p < 0.001$	
Ischemic heart disease, n (%)	1	(1.3%)	2	(1.7%)	24	(22.6%)	$p < 0.001$	
Atrial fibrillation, n (%)	1	(1.3%)	8	(6.8%)	18	(17.0%)	$p < 0.001$	
Chronic kidney disease, n (%)	7	(9.2%)	43	(36.4%)	50	(47.2%)	$p < 0.001$	
COPD, n (%)	9	(11.8%)	18	(15.3%)	16	(55.7%)	$p = 0.773$	
Sleep apnea, n (%)	1	(1.3%)	9	(7.6%)	7	(6.6%)	$p = 0.154$	
Smoking, n (%)	8	(10.5%)	15	(12.7%)	15	(14.2%)	$p = 0.769$	
Cerebrovascular disease, n (%)	0	(0.0%)	1	(0.8%)	26	(24.5%)	$p < 0.001$	
Active malignancy, n (%)	2	(2.6%)	8	(6.8%)	10	(9.4%)	$p = 0.194$	
Scores								
M-CHADSVASc, median (Q1 - Q3) (points)	1	(1 - 1)	2	(2 - 3)	5	(4 - 5)	$p < 0.001$	Group 1 *vs* 2: $p < 0.001$ Group 1 *vs* 3: $p < 0.001$ Group 2 *vs* 3: $p < 0.001$
CHADSVASc, median (Q1 - Q3) (points)	1	(0 - 2)	2	(1 - 3)	4	(3 - 5)	$p < 0.001$	Group 1 *vs* 2: $p < 0.001$ Group 1 *vs* 3: $p < 0.001$ Group 2 *vs* 3: $p < 0.001$
Laboratory results								
D-dimer, median (Q1 - Q3) (ng/mL)	1020	(640 - 1910)	1710	(890 - 4340)	2110	(1120 - 6270)	$p < 0.001$	Group 1 *vs* 2: $p < 0.001$ Group 1 *vs* 3: $p < 0.001$ Group 2 *vs* 3: $p = 0.217$
cTnT-hs, median (Q1 - Q3) (ng/L)	6	(4 - 10)	18.5	(10.8 - 31.8)	32	(18 - 64.5)	$p < 0.001$	Group 1 *vs* 2: $p < 0.001$ Group 1 *vs* 3: $p < 0.001$ Group 2 *vs* 3: $p < 0.001$
NT-proBNP, median (Q1 - Q3) (pg/mL)	65	(28 - 226)	488	(168 - 1383)	806	(332 - 2944)	$p < 0.001$	Group 1 *vs* 2: $p < 0.001$ Group 1 *vs* 3: $p < 0.001$ Group 2 *vs* 3: $p = 0.049$
Creatinine, median (Q1 - Q3) (mg/dl)	0.86	(0.71 - 1.04)	0.97	(0.82 - 1.22)	1.11	(0.88 - 1.64)	$p < 0.001$	Group 1 *vs* 2: $p = 0.004$ Group 1 vs 3: $p < 0.001$ Group 2 *vs* 3: $p = 0.007$
eGFR, median (Q1 - Q3) (mL/min/1.73m^2)	90	(73 - 102)	73	(52 - 88)	60	(38 - 78)	$p < 0.001$	Group 1 *vs* 2: $p < 0.001$ Group 1 *vs* 3: $p < 0.001$ Group 2 *vs* 3: $p = 0.001$
Clinical outcomes								
Pulmonary embolism, n (%)	9	(11.8%)	21	(17.8%)	16	(15.1%)	$p = 0.531$	
Hospitalization, n (%)	59	(77.6%)	99	(83.9%)	91	(85.8%)	$p = 0.329$	
ICU admission, n (%)	12	(15.8%)	18	(15.3%)	19	(17.9%)	$p = 0.730$	
Invasive mechanical ventilation, n (%)	8	(10.5%)	14	(11.9%)	14	(13.2%)	$p = 0.736$	
Death, n (%)	6	(7.9%)	24	(20.3%)	39	(36.8%)	$p < 0.001$	

COPD: chronic obstructive pulmonary disease; cTnT-hs. high-sensitive Troponin T; NT-proBNP: N-terminal prohormone BNP; eGFR: estimated glomerular filtration rate; ICU: intensive care unit

had bilateral involvement (57%) and 22% of patients had evidence of right heart strain on CTPA (defined as right /left ventricle ratio > 1 or interventricular septal bowing). None of the patients with PE presented with hemodynamic instability attributable to PE and therefore thrombolytic therapy was not administrated in any patient.

We found no difference in PE incidence according to the M-CHA_2DS_2-VASc risk stratification (p = 0.531) – Table 2. Additionally, M-CHA_2DS_2-VASc showed no predictive value for PE occurrence (OR: 1.050, 95% CI 0.878 - 1.255, p = 0.596). A ROC analysis produced an AUC of 0.52 (95%CI 0.43 - 0.61, p = 0.703) and 0.56 (95% CI 0.47 - 0.65, p = 0.188) for M-CHA_2DS_2-VASc and CHA_2DS_2-VASc, respectively, suggesting that both scores had nearly no discriminative power to predict PE (with no difference in the discriminative capacity between both scores: z test = 1.625, p = 0.104).

The univariate analysis identified cTnT-hs (OR: 1.007, 95% CI 1.002 - 1.012, p = 0.011), D-dimer (OR: 1.018, 95% IC 1.004 - 1.031, p = 0.010) and older age (OR: 1.024, 95% IC 1.002 - 1.047, p = 0.036) as predictors of PE.

Neither M-CHA_2DS_2-VASc nor CHA_2DS_2-VASc demonstrated predictive value for ICU admission or need for invasive mechanical ventilation (p = 0.730 and p = 0.736; p = 0.236 and p = 0.480, respectively).

COVID-19 patient survivors versus non-survivors

A comparison of baseline characteristics of COVID-19 patient survivors and non-survivors is shown in Table 1. Non-survivors were older [81 (IQR 73 - 88) *vs* 69 (IQR 56 - 78) years, p < 0.001] and had higher prevalence of cardiovascular risk factors such as hypertension (69% *vs* 55%, p = 0.034), chronic kidney disease (46% *vs* 29%, p = 0.008) and history of smoking (20% *vs* 10%, p = 0.044).

Although both M-CHA_2DS_2-VASc and CHA_2DS_2-VASc scores were higher in non-survivors compared to survivors (p < 0.001), the M-CHA_2DS-VASc score showed better predictive value for short-term mortality (AUC 0.71 *vs* 0.67; z test = 2.06; p = 0.039).

Despite being elevated in all patients, non-survivors had higher D-dimer, cTnT-hs and NTpro-BNP levels compared to survivors (p < 0.001 for all).

As mentioned above, the incidence of PE was similar in both survivors and non-survivors (14% *vs* 16%, p = 0.369). On the other hand, ICU admission and the need for invasive mechanical ventilation were more frequent in the non-survivors group (27% *vs* 12%, p = 0.002; 25% *vs* 7%, p < 0.001, respectively).

Risk stratification according to M-CHA_2DS_2-VASc

We divided the cohort into three subgroups based on the M-CHA_2DS_2-VASc score: 0 - 1, 2 - 3 and ≥ 4 points, corresponding to low, intermediate, and high-risk groups for adverse clinical outcomes, respectively. A total of 106 patients (35.3%) were included in the higher risk group, 118 patients (39.3%) in the intermediate-risk group and 76 patients (25.3%) in the lower risk group. The patient characteristics stratified according to the M-CHA_2DS_2-VASc score risk-groups are shown in Table 2.

Patients with higher M-CHA_2DS_2-VASc score were older, mostly male, and had a higher prevalence of comorbidities, such as dyslipidemia, diabetes, chronic heart

Table 3 – Univariable and multivariable predictors of in hospital and short-term mortality

	Univariate			Multivariable		
	Odds Ratio (95% CI)		*p* value	Odds Ratio (95% CI)		*p* value
M-CHA_2DS_2-VASc (continuous variable)	1.56	(1.33 - 1.84)	p < 0.001	1.41	(1.10 - 1.81)	p = 0.007
CHA_2DS_2VASc (continuous variable)	1.43	(1.22 - 1.67)	p < 0.001			
Age	1.08	(1.05 - 1.10)	p < 0.001			
Male gender	1.59	(0.93 - 2.71)	p = 0.088			
Hypertension	1.81	(1.06 - 3.12)	p = 0.031			
Diabetes mellitus	1.24	(0.71 - 2.17)	p = 0.452			
Vascular disease	1.40	(0.60 - 3.25)	p = 0.439			
Cerebrovascular disease	2.77	(1.24 - 6.19)	p = 0.013			
Heart failure	1.59	(0.67 - 3.75)	p = 0.293			
Chronic ischemic disease	1.40	(0.60 - 3.25)	p = 0.439			
Obesity	0.78	(0.39 - 1.57)	p = 0.484			
Chronic kidney disease	2.08	(1.23 - 3.52)	p = 0.006	0.89	(0.37 - 2.15)	p = 0.798
Smoking	2.20	(1.09 - 4.45)	p = 0.027	1.69	(0.58 - 4.94)	p = 0.338
COPD	1.06	(0.51 - 2.17)	p = 0.885			
cTnT-hs	1.007	(1.001 - 1.013)	p = 0.014	1.005	(1.000 - 1.011)	p = 0.072
NT-proBNP	1.000	(1.000 - 1.000)	p = 0.177			
D-Dimer	1.003	(0.997 - 1.010)	p = 0.301			

CI: confidence interval; COPD: chronic obstructive pulmonary disease; cTnT-hs: high-sensitive Troponin T; NT-proBNP: N-terminal prohormone BNP

failure, ischemic heart disease, cerebrovascular disease and chronic kidney disease ($p < 0.001$ for all). High-sensitive troponin T increased progressively from a lower to higher M-CHA_2DS_2-VASc score ($p < 0.001$). Both D-dimer and NTpro-BNP levels were significantly lower in patients with M-CHA_2DS_2-VASc score ≤ 1 compared to the patients with intermediate or high-risk ($p < 0.001$ for both).

Regarding mortality, we found that the M-CHA_2DS_2-VASc score was significantly higher in COVID-19 patient non-survivors compared to survivors [4 (IQR 3 - 5) *vs* 2 (IQR 1 - 4), respectively, $p < 0.001$]. A multivariable logistic regression analysis was performed for mortality based on the following variables: M-CHA_2DS_2-VASc, cTnT-hs, chronic kidney disease and smoking history. Among these variables, M-CHA_2DS_2-VASc was identified as an independent predictor of mortality in COVID-19 patients (OR: 1.406, 95% IC 1.096 - 1.805, $p = 0.007$). The model did not include the CHA_2DS_2-VASc score because it contained similar variables to the M-CHA_2DS_2-VASc score. In addition, it did not include age, hypertension, and cerebrovascular disease because those variables were included in the M-CHA_2DS_2-VASc score. The results of the univariate and multivariable logistic regression analysis were demonstrated in Table 3.

The survival proportion by Kaplan-Meier analysis showed that M-CHA_2DS_2-VASc score was directly and incrementally associated with reduced survival. The overall estimated survival proportions were 92.1% in the lower M-CHA_2DS_2-VASc risk group, 79.66% in the intermediate risk group and 63.21% in the higher risk group (log-rank test $p < 0.001$; Fig. 1A).

Although most patients in the cohort were hospitalized, 51 patients were discharged from the ED (17%). Among these patients, 33.3% (n = 17) had low risk, 37.2% (n = 19) intermediate risk and 29.4% (n = 15) high risk for mortality according to the M-CHA_2DS_2-VASc score risk-stratification. The Kaplan-Meier individual survival analysis for hospitalized patients (Fig. 1B) and for those discharged from the ED (Fig. 1C) revealed that the M-CHA_2DS_2-VASc score maintains a good discriminative ability to predict short-term mortality for both groups (log-rank test $p < 0.001$ and log-rank test $p = 0.007$, respectively).

The ROC analysis comparing the accuracy of M-CHA_2DS_2-VASc, CHA_2DS_2-VASc, cTnT-hs and NTpro-BNP to predict mortality is shown in Fig. 2. The AUC for M-CHA_2DS_2-VASc, CHA_2DS_2-VASc, cTnT-hs and NTpro-BNP were 0.71 (95% CI 0.64 - 0.77), 0.67 (95% CI 0.60 - 0.74), 0.62 (95% CI 0.56 - 0.67) and 0.57 (95% CI 0.51 - 0.62), respectively ($p < 0.001$ for all). The pair-wise comparison of ROC curves showed that M-CHA_2DS_2-VASc had better predictive value for short-term mortality than CHA_2DS_2-VASc (z test = 2.06, $p = 0.039$), cTnT-hs (z test = 2.21, $p = 0.027$) and NTpro-BNP (z test = 3.26, $p = 0.001$). With a cut-off value of 2.5, the M-CHA_2DS_2-VASc score had a sensitivity of 75% and a specificity of 53% to predict short-term mortality.

DISCUSSION

The results of our study suggest that the recently proposed M-CHA_2DS_2-VASc score has a good discriminative ability to predict short-term mortality in COVID-19 patients admitted to the ED, although it was not a predictor of PE occurrence, ICU admission or invasive mechanical ventilation. To the best of our knowledge, this is the first study to validate this score as a predictor of mortality in COVID-19 patients admitted to the ED, whether they were hospitalized or not, and to further demonstrate its prognostic value as a predictor of short-term mortality.

The CHA_2DS_2-VASc score is well-validated for thromboembolic risk-stratification and its ability to predict mortality has been demonstrated in several cardiovascular conditions.[5–8] In addition, several individual risk factors included in the CHA_2DS_2-VASc score have also been recognized as risk factors for COVID-19 related mortality, such as older age, hypertension, diabetes, coronary artery disease and cerebrovascular disease.[9–11] Based on this knowledge, a study conducted by Quisi *et al* reported a high predictive value of CHA_2DS_2-VASc for in-hospital mortality in a cohort of 349 hospitalized COVID-19 patients.[15]

Considering that the male gender was previously identified as a risk factor for COVID-19 mortality,[13] Cetinkal *et al* improved the discriminative performance of CHA_2DS_2-VASc score by creating the modified score (M-CHA_2DS_2-VASc), which is based on changing gender criteria from female to male.[12] The authors validated the new proposed score as an independent predictor of in-hospital mortality in a cohort of 717 hospitalized COVID-19 patients, demonstrating a better predictive value compared to the CHA_2DS-VASc score. Recently, Gunduz *et al* also showed the predictive value of the M-CHA_2DS_2-VASc score for ICU admission.[16] Consistent with these results, we demonstrated that the M-CHA_2DS_2-VASc score was an independent predictor of mortality in COVID-19 patients (OR: 1.406, 95% IC 1.096 - 1.805, $p = 0.007$). In our cohort, COVID-19 patient non-survivors had significantly higher M-CHA_2DS_2-VASc [4 (IQR 3 - 5) *vs* 2 (IQR 1 - 4), respectively, $p < 0.001$] compared to survivors. The overall estimated survival proportions were 92%, 80% and 63% for patients with M-CHA_2DS_2-VASc of ≤ 1, 2 - 3 and ≥ 4 points, respectively.

Although the M-CHA_2DS_2-VASc score was previously validated to predict in-hospital mortality in a cohort of hospitalized patients, we also demonstrated its predictive value for patients admitted to the ED, whether hospitalized or not, and its ability to predict short-term mortality. This additional ability highlights once again the contribution of the patient's overall cardiovascular condition on survival and explains why the score is still valid for outpatients.

Previous studies revealed that myocardial injury was associated with adverse clinical outcomes in COVID-19 patients, including mortality.[17] Although elevated in all cohorts, we found that D-dimer, cTnT-hs and NTpro-BNP levels were significantly higher in non-survivors compared to survivors ($p < 0.001$ for all). Besides, patients with M-CHA_2DS_2-VASc ≥ 4 had significantly higher cTnT-hs and NTpro-BNP

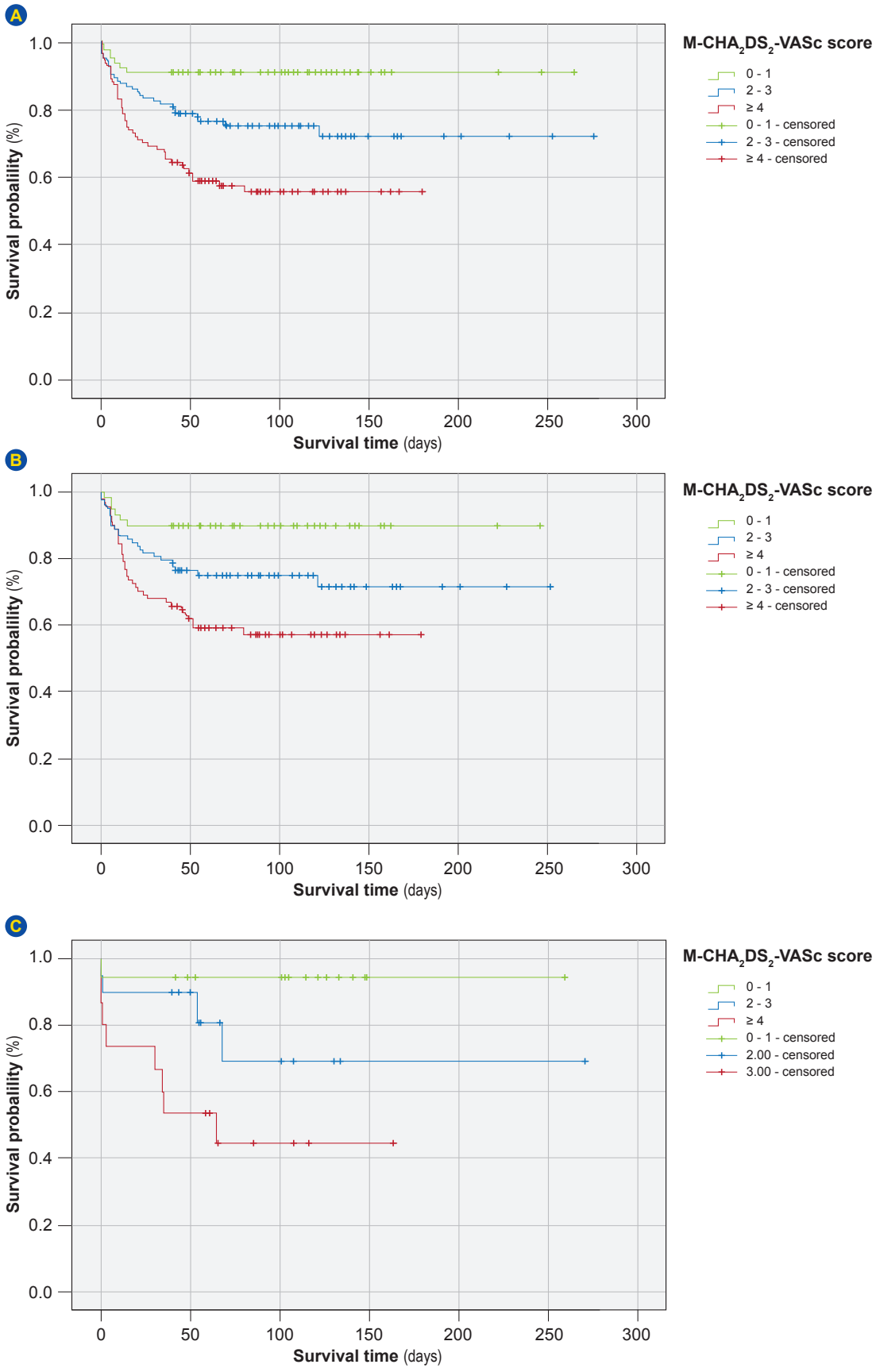
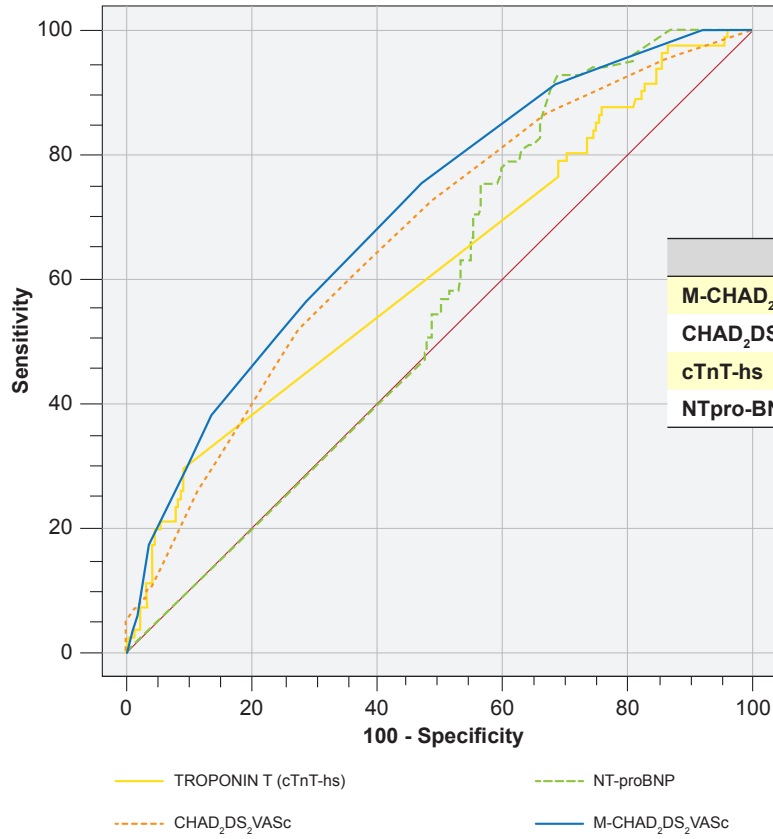


Figure 1 – Kaplan-Meier survival analysis stratified by terciles of M-CHA_2DS_2-VASc score: low risk (0 - 1 points), intermediate risk (2 - 3 points) and high risk (≥ 4). (A) All cohort (n = 300); log-Rank $p < 0.001$; (B) Hospitalized patients (n = 249); log rank $p < 0.001$; (C) Discharged patients from emergency department (n = 51); log-Rank $p = 0.007$.



	AUC (95% CI)	*p* value
M-CHAD$_2$DS$_2$-VASc	**0.71** (0.64 - 0.77)	$p < 0.001$
CHAD$_2$DS$_2$-VASc	**0.67** (0.60 - 0.74)	$p < 0.001$
cTnT-hs	**0.62** (0.56 - 0.67)	$p < 0.001$
NTpro-BNP	**0.57** (0.51 - 0.62)	$p < 0.001$

Figure 2 – ROC analysis comparing the predictive accuracy of M-CHA$_2$DS$_2$-VASc, CHA$_2$DS$_2$-VASc, high-sensitive troponin (cTnT-hs) and N-terminal prohormone BNP (NT-proBNP)
AUC: area under the curve; CI: confidence interval

levels than patients with M-CHA$_2$DS-VASC < 4 ($p < 0.001$ and $p = 0.049$, respectively), suggesting that these patients are more susceptible to myocardial injury. These findings highlight the role of cardiovascular risk factors in the pathophysiology and prognosis of COVID-19 patients.

As for adverse clinical outcomes other than mortality, the M-CHA$_2$DS$_2$-VASc score showed no predictive value for PE occurrence, admission to the ICU or need for invasive mechanical ventilation ($p = 0.531$, $p = 0.730$ and $p = 0.736$, respectively).

The PE incidence was 15%, which is consistent with the literature published so far.[14,18–20] In line with the previous studies,[14,21,22] we found no differences regarding comorbidities or risk factors for venous thromboembolism between PE and non-PE patients, which may justify the absence of predictive value of M-CHA$_2$DS$_2$-VASc and CHA$_2$DS$_2$-VASc for PE occurrence. This data highlights the difficulty of PE risk stratification in COVID-19 patients, probably because inflammation, endothelial dysfunction and coagulopathy play a major role in its pathophysiology.[17] In addition, we found that the incidence of PE was similar in both survivors and non-survivors (14% *vs* 16%, $p = 0.369$), suggesting that PE may not be the main determinant of mortality in these patients. However, although our findings concur with those of a large French multicentre cohort of 1240 patients,[14] other studies documented a higher mortality risk among patients with PE.[23,24]

Moreover, for in-hospital mortality in COVID-19 patients[12], our study also revealed the superiority of M-CHA$_2$DS$_2$-VASc in predicting short-term mortality in patients admitted to the ED, compared to CHA$_2$DS-VASc. Neither of the scores was a reliable predictor for PE, ICU admission and invasive mechanical ventilation.

The mortality rate observed (27%) was comparable with previous reports, regardless of the heterogeneity among populations studied.[25,26] Considering that patient selection was based on CTPA request due to clinical worsening and/or PE suspicion, it is probable that our cohort included patients with more severe disease, which is reinforced by the high rate of hospitalization and ICU admission documented in our cohort.

Considering there is a lack of well-validated scores to predict mortality in COVID-19 patients, the M-CHA$_2$DS$_2$-VASc might be a simple and easily available clinical score for mortality risk-stratification. In addition, it has the advantage of not including laboratory or imaging data, allowing it to be applied at the point of care during hospital admission or even in the primary healthcare setting. Besides, its predictive value in ED discharged patients suggests that it might be helpful to signal patients in need of a closer follow-up.

Limitations

Our study must be evaluated in light of some limitations.

First, this is a single-centre retrospective observational study. Therefore, larger, prospective multicentre studies are needed in order to draw more definitive conclusions. Second, we included patients who underwent CTPA due to clinical worsening or PE suspicion, which may represent a cohort with more severe disease. Thus, it may not be representative of the general population. Third, an analysis of the cause of death was not performed. Lastly, some of the score parameters might not have been fully recorded in all patients. However, we had only 2% of missing data burden.

CONCLUSION

To the best of our knowledge, our study was the first to validate M-CHA_2DS_2-VASc score as a predictor of short-term mortality in patients with COVID-19 admitted to the emergency department, regardless of whether they were hospitalized or not. Therefore, this score is a simple tool that may be useful for prompt risk stratification during ED admission, allowing the identification of high-risk patients who would benefit from specific treatment and closer follow-up strategies.

AUTHORS CONTRIBUTION

BVS: Conceived the idea, analyzed the data and took the lead in writing the manuscript.

CM, MLU, JB, PAS: Collected data.

CJ, RP, JR, TR, FJP: Supported and reviewed the manuscript.

All authors provided critical feedback and helped shaped the research, analysis and manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

None.

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