








Prediction of thromboembolic events and mortality by the CHADS₂ and the CHA₂DS₂-VASc in COVID-19

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Aims

Age, sex, and cardiovascular disease have been linked to thromboembolic complications and poorer outcomes in COVID-19. We hypothesize that CHADS₂ and CHA₂DS₂-VASc scores may predict thromboembolic events and mortality in COVID-19.

Methods and results

COVID-19 hospitalized patients with confirmed SARS-CoV-2 infection from 1 March to 20 April 2020 who completed at least 1-month follow-up or died were studied. CHADS₂ and CHA₂DS₂-VASc scores were calculated. Given the worse prognosis of male patients in COVID-19, a modified CHA₂DS₂-VASc score (CHA₂DS₂-VASc-M) in which 1 point was given to male instead of female was also calculated. The associations of these scores with laboratory results, thromboembolic events, and death were analysed. A total of 3042 patients (mean age 62.3 ± 20.3 years, 54.9% male) were studied and 115 (3.8%) and 626 (20.6%) presented a definite thromboembolic event or died, respectively, during the study period [median follow 59 (50–66) days]. Higher score values were associated with more marked abnormalities of inflammatory and cardiac biomarkers. Mortality was significantly higher with increasing scores for CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M ($P < 0.001$ for trend). The CHA₂DS₂-VASc-M showed the best predictive value for mortality [area under the receiver operating characteristic curve (AUC) 0.820, $P < 0.001$ for comparisons]. All scores had poor predictive value for thromboembolic events (AUC 0.497, 0.490, and 0.541, respectively).

Conclusion

The CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M scores are significantly associated with all-cause mortality but not with thromboembolism in COVID-19 patients. They are simple scoring systems in everyday use that may facilitate initial 'quick' prognostic stratification in COVID-19.

Keywords

COVID-19 • CHADS₂ • CHA₂DS₂-VASc • Thromboembolism • Mortality

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What's new?

- Major concern exists regarding a prothrombotic state complicating the clinical course of COVID-19. However, useful tools for the prediction of thromboembolic events are lacking.
- Using data from a large cohort of confirmed patients, we proved that CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M (a modified CHA₂DS₂-VASc score in which one point is given to male sex, instead of female sex) show extremely poor value for the prediction of thromboembolic events.
- Interestingly, these scoring systems adequately predicted all-cause mortality during follow-up.
- CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M are simple scoring systems that may facilitate prognostic stratification in COVID-19 patients at the moment of first medical contact.

Introduction

The ongoing COVID-19 pandemic poses a significant challenge to most healthcare systems around the world. While respiratory failure remains the most common reason for admission to critical care units and death, SARS-CoV-2 infection has proven to be a complex condition with multiorgan involvement.

Since the beginning of the pandemic, data from China and Italy suggested a significant prevalence of cardiovascular (CV) risk factors among hospitalized and critically ill patients with COVID-19.¹ Age and underlying CV disease² are associated with poorer outcomes and thromboembolic complications play a key role in the clinical course of these patients.³

The CHADS₂ and CHA₂DS₂-VASc scores are simple clinical scores based on age, sex, CV risk factors, and underlying cardiovascular disease, widely employed to stratify the risk of systemic thromboembolic complications in patients with atrial fibrillation (AF).⁴ In addition, the CHADS₂ and CHA₂DS₂-VASc scores also predict mortality in various conditions, whether they present with or without AF.⁵ This should not be considered surprising since the CHADS₂ and CHA₂DS₂-VASc scores are clusters of common cardiovascular risk factors that have prognostic implications, irrespective of the presence of AF. The prognostic value of these scores in COVID-19 is unknown.

In patients with SARS-CoV-2 infection, there is the need to have a simple and practical approach to clinical prognostication, especially for the risks of mortality and thromboembolism. More complex prognostic scores have been proposed, with varying practicality and clinical applicability for clinical management and decision making.⁶ In very busy settings, e.g., during the peak of the pandemic, easy and practical risk assessment tools are essential. The aim of this study was to assess the value of the CHADS₂ and CHA₂DS₂-VASc scores to predict thromboembolic events and all-cause mortality in patients with COVID-19. Secondly, we explored the value of giving extra weight to male sex in the CHA₂DS₂-VASc score, given the extra risk associated with males compared with females.¹

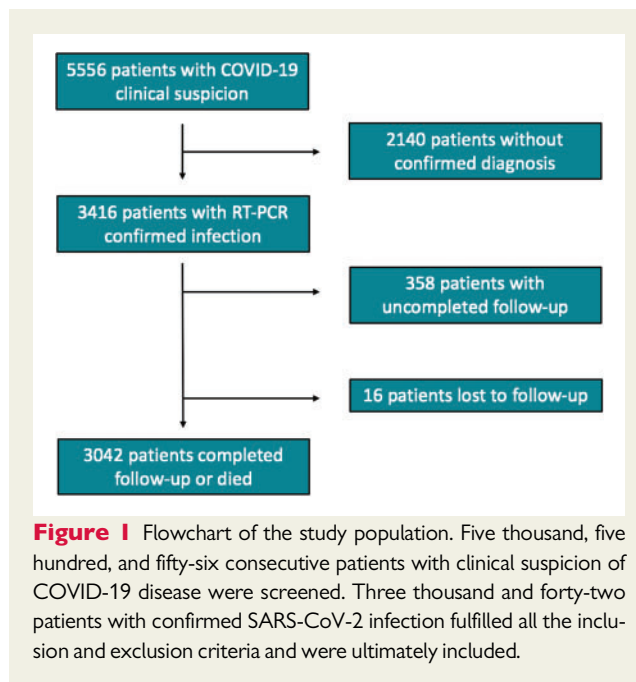


Figure 1 Flowchart of the study population. Five thousand, five hundred, and fifty-six consecutive patients with clinical suspicion of COVID-19 disease were screened. Three thousand and forty-two patients with confirmed SARS-CoV-2 infection fulfilled all the inclusion and exclusion criteria and were ultimately included.

Methods

Study design and participants

We screened all consecutive patients with clinical suspicion of COVID-19 attended at the Emergency Room in a tertiary care centre in Madrid from 1 March 2020 to 20 April 2020. Patients were only included in the study if they had confirmation of SARS-CoV-2 infection by RNA reverse-transcriptase–polymerase chain reaction assay of nasal or pharyngeal swab specimens. We aimed to include patients who have completed a follow-up of at least 30 days since their diagnosis. Therefore, patients who were alive and diagnosed <30 days before the lock of the database were excluded from the present analysis. The present study was approved by our Institutional Review Board. Individual written informed consent was waived based on legal standards for national healthcare alarm situations.

Data collection

Epidemiological, demographic, clinical, laboratory, treatment, and outcome data were extracted from electronic medical records from the index and subsequent hospital admissions using a standardized electronic data collection form. In addition, the central healthcare record system, which collects information and medical reports from all public hospitals and primary healthcare centres from the Madrid region, was reviewed for additional information and follow-up. All data were thoroughly reviewed by a team of 13 cardiologists. Special care was given to the identification of CV baseline characteristics and outcomes.

Study definitions and objectives

The CHADS₂ score ranging from 0 to 6 was calculated for each patient as congestive heart failure or left ventricular ejection fraction $\leq 40\%$ (1 point); hypertension (1 point); age ≥ 75 years (1 point); and history of stroke, transient ischaemic attack (TIA), or systemic embolism (2 points). The CHA₂DS₂-VASc⁴ score was calculated by assigning 2 points for age ≥ 75 and history of stroke, TIA, or thromboembolism and 1 point for congestive heart failure, hypertension, diabetes mellitus, age 65–75 years,

Table 1 Characteristics of study patients with and without thrombotic events

Variables	All (N = 3042)	Non-thrombotic event (n = 2927)	Thrombotic event (n = 115)	P-value
Age (years)	62.3 ± 20.3	62.1 ± 20.5	67.3 ± 11.6	0.007
Male sex	1670 (54.9%)	1595 (54.5%)	75 (65.2%)	0.023
Time from symptom onset to diagnosis (days)	6.2 ± 5.3	6.2 ± 5.3	7.4 ± 5.6	0.019
Hypertension	1309 (43.0%)	1253 (42.9%)	56 (48.7%)	0.219
Diabetes	556 (18.3%)	534 (18.4%)	22 (19.3%)	0.798
Dyslipidaemia	1090 (35.8%)	1043 (36.9%)	47 (41.6%)	0.313
Tobacco use	298 (9.8%)	286 (9.8%)	12 (10.4%)	0.814
Coronary heart disease	196 (6.4%)	190 (6.5%)	6 (5.2%)	0.573
Heart failure	150 (4.9%)	147 (5.0%)	3 (2.6%)	0.375
Atrial fibrillation	249 (8.1%)	244 (8.3%)	5 (4.4%)	0.163
Atrial flutter	23 (0.8%)	21 (0.7%)	2 (1.7%)	0.215
ICD/pacemaker	52 (1.7%)	50 (1.7%)	2 (1.7%)	1.000
Stroke or TIA	185 (6.1%)	182 (6.3%)	3 (2.6%)	0.160
Peripheral artery disease	197 (6.5%)	187 (6.4%)	10 (8.7%)	0.337
COPD	234 (7.6%)	223 (7.6%)	11 (9.6%)	0.442
BMI	28.3 ± 5.3	28.3 ± 5.3	28.6 ± 5.6	0.672
Cancer	300 (9.9%)	285 (9.7%)	15 (13.0%)	0.243
Chronic kidney disease	179 (5.9%)	171 (5.8%)	8 (7.0%)	0.618
Anticoagulation	307 (10.1%)	297 (10.2%)	10 (8.7%)	0.597
Antiplatelets	434 (14.3%)	422 (14.4%)	12 (10.4%)	0.231
ACE inhibitor	574 (18.9%)	555 (19.0%)	19 (16.5%)	0.512
ARB	425 (14.0%)	405 (13.8%)	20 (17.4%)	0.281
β-blockers	406 (13.4%)	394 (13.5%)	12 (10.4%)	0.349
Aldosterone antagonists	92 (3.0%)	90 (3.1%)	2 (1.7%)	0.582
iSGLT2	42 (1.4%)	39 (1.3%)	3 (2.6%)	0.211
Statins	869 (28.6%)	833 (28.5%)	36 (31.3%)	0.508
Digoxin	22 (0.7%)	20 (0.7%)	2 (1.7%)	0.201
SatO ₂ at admission	92.2 ± 6.2	92.3 ± 6.1	89.3 ± 7.5	<0.001
Supplemental O ₂ at first SatO ₂ assessment	281 (9.2%)	254 (8.7%)	27 (23.5%)	<0.001
Chest radiography ^a				
No pneumonia	809 (26.6%)	799 (27.3%)	10 (8.7%)	
Unilateral pneumonia	583 (19.2%)	569 (19.4%)	14 (12.2%)	<0.001
Bilateral pneumonia	1528 (50.2%)	1437 (49.1%)	91 (79.1%)	
NT-proBNP above cut points for AHF ^b	188 (6.2%)	158 (5.4%)	30 (26.1%)	<0.001
D-dimer >1000 ng/mL	992 (32.6%)	886 (30.3%)	106 (92.2%)	<0.001
Hydroxychloroquine	2361 (77.6%)	2250 (76.9%)	111 (96.5%)	<0.001
Azithromycin	1390 (45.7%)	1306 (44.6%)	84 (73.0%)	<0.001
Lopinavir/ritonavir	319 (10.4%)	309 (10.6%)	10 (8.7%)	0.523
Tocilizumab	227 (7.5%)	178 (6.1%)	49 (42.6%)	<0.001
Corticoids	440 (14.5%)	387 (13.2%)	53 (46.1%)	<0.001
Hospital stay (days)	9.1 ± 10.2	8.6 ± 9.6	24.5 ± 14.3	<0.001
Major bleeding	21 (0.7%)	15 (0.5%)	6 (5.2%)	<0.001
Thromboembolic event	115 (3.8%)	69 (2.9%)	46 (7.4%)	<0.001
Arrhythmias	117 (3.9%)	97 (3.3%)	20 (17.4%)	<0.001
Mechanical ventilation	171 (5.6%)	74 (5.5%)	28 (39.4%)	<0.001
Death	626 (20.6%)	580 (19.8%)	46 (40.0%)	<0.001

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICD, implantable cardiac-defibrillator; iSGLT2, sodium-glucose co-transporter 2 inhibitors; TIA, transient ischaemic attack.

^aTwo thousand, nine hundred, and twenty patients underwent chest radiography.

^bAbnormal NT-proBNP levels according to recommended cut-off values of the Heart Failure Association of the European Society of Cardiology (ESC): >450 pg/mL in patients below 50 years, >900 pg/mL in patients between 50 and 75 years, and >1800 pg/mL in patients over 75 years.

Table 2 Characteristics of study patients according to vital status at 1 month

Variables	All (N = 3042)	Survivors (n = 2416)	Non-survivors (n = 626)	P-value
Age (years)	62.3 ± 20.3	57.6 ± 19.5	80.5 ± 11.0	<0.001
Male sex	1670 (54.9%)	1274 (52.7%)	396 (63.3%)	<0.001
Time from symptom onset to diagnosis (days)	6.2 ± 5.3	6.5 ± 5.4	5.0 ± 4.8	<0.001
Hypertension	1309 (43.0%)	872 (36.1%)	437 (69.8%)	<0.001
Diabetes	556 (18.3%)	360 (14.9%)	196 (31.3%)	<0.001
Dyslipidaemia	1090 (35.8%)	744 (30.8%)	346 (55.3%)	<0.001
Tobacco use	298 (9.8%)	219 (9.1%)	79 (12.6%)	0.019
Coronary heart disease	196 (6.4%)	116 (4.8%)	80 (12.8%)	<0.001
Heart failure	150 (4.9%)	76 (3.2%)	74 (11.8%)	<0.001
Atrial fibrillation	249 (8.1%)	120 (5.0%)	129 (20.6%)	<0.001
Atrial flutter	23 (0.8%)	11 (0.5%)	12 (1.9%)	0.001
ICD/pacemaker	52 (1.7%)	21 (0.9%)	31 (5.0%)	<0.001
Stroke or TIA	185 (6.1%)	90 (3.7%)	95 (15.2%)	<0.001
Peripheral artery disease	197 (6.5%)	99 (4.1%)	98 (15.7%)	<0.001
COPD	234 (7.6%)	140 (5.8%)	94 (15.0%)	<0.001
BMI	28.3 ± 5.3	28.2 ± 5.4	28.9 ± 4.8	0.025
Cancer	300 (9.9%)	189 (7.8%)	111 (17.7%)	<0.001
Chronic kidney disease	179 (5.9%)	83 (3.4%)	96 (15.3%)	<0.001
Anticoagulation	307 (10.1%)	157 (6.5%)	150 (24.0%)	<0.001
Antiplatelets	434 (14.3%)	254 (10.5%)	180 (28.8%)	<0.001
ACE inhibitor	574 (18.9%)	398 (16.5%)	176 (28.1%)	<0.001
ARB	425 (14.0%)	287 (11.9%)	138 (22.0%)	<0.001
β-Blockers	406 (13.4%)	251 (10.4%)	155 (24.8%)	<0.001
Aldosterone antagonists	92 (3.0%)	51 (2.1%)	41 (6.6%)	<0.001
iSGLT2	42 (1.4%)	29 (1.2%)	13 (2.1%)	0.094
Statins	869 (28.6%)	586 (24.3%)	283 (45.2%)	<0.001
Digoxin	22 (0.7%)	7 (0.3%)	15 (2.4%)	<0.001
SatO ₂ at admission	92.2 ± 6.2	93.5 ± 4.1	87.7 ± 9.5	<0.001
Supplemental O ₂ at first SatO ₂ assessment	281 (9.2%)	138 (5.7%)	143 (2.8%)	<0.001
Chest radiography ^a				
No pneumonia	809 (26.6%)	724 (30.0%)	85 (13.6%)	
Unilateral pneumonia	583 (19.2%)	471 (19.5%)	112 (17.9%)	<0.001
Bilateral pneumonia	1528 (50.2%)	1120 (46.4%)	408 (65.2%)	
NT-proBNP above cut points for AHF ^b	188 (6.2%)	79 (3.3%)	109 (17.4%)	<0.001
D-dimer >1000 ng/mL	992 (32.6%)	646 (26.7%)	346 (55.3%)	<0.001
Hydroxychloroquine	2361 (77.6%)	1828 (75.7%)	533 (85.1%)	<0.001
Azithromycin	1390 (45.7%)	1096 (45.4%)	294 (47.0%)	0.474
Lopinavir/ritonavir	319 (10.4%)	234 (9.7%)	85 (13.6%)	0.007
Tocilizumab	227 (7.5%)	167 (6.9%)	60 (9.6%)	0.023
Corticosteroids	440 (14.5%)	234 (9.7%)	206 (32.9%)	<0.001
Hospital stay (days)	9.1 ± 10.2	9.0 ± 10.4	9.9 ± 9.0	0.145
Thrombotic event	115 (3.8%)	69 (2.9%)	46 (7.4%)	<0.001
Major bleeding	21 (0.7%)	9 (0.4%)	12 (1.9%)	<0.001
Arrhythmias	117 (3.9%)	47 (2.0%)	70 (11.2%)	<0.001
Mechanical ventilation	171 (5.6%)	74 (3.1%)	97 (15.5%)	<0.001

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; BMI body mass index; COPD, chronic obstructive pulmonary disease; ICD, implantable cardiac-defibrillator; iSGLT2, sodium-glucose co-transporter 2 inhibitors; TIA, transient ischaemic attack.

^aTwo thousand, nine hundred, and twenty patients underwent chest radiography.

^bAbnormal NT-proBNP levels according to recommended cut-off values of the Heart Failure Association of the European Society of Cardiology (ESC): >450 pg/mL in patients below 50 years, >900 pg/mL in patients between 50 and 75 years, and >1800 pg/mL in patients over 75 years.

vascular disease, and female sex category. Given that male sex has been identified as a poor prognostic factor in COVID-19 disease,¹ we additionally explored if the use of a modified version of the CHA₂DS₂-VASc scoring system (CHA₂DS₂-VASc-M) in which 1 point was assigned to male sex instead of female sex provided an enhanced risk prediction.

The primary endpoint of the present study was occurrence of a thromboembolic event. Definite thromboembolic events during follow-up were defined as the diagnosis of deep vein thrombosis, pulmonary embolism, stroke, or acute coronary syndrome based on appropriate imaging criteria. All-cause mortality was considered a coprimary endpoint. The leading cause of death was defined from the electronic medical records. Major bleeding was defined as specified in the Thrombolysis in Myocardial Infarction bleeding classification⁷ (drop in haemoglobin ≥ 5 g/dL, intracranial, or fatal bleeding). In-hospital prescriptions of anticoagulation treatment were confirmed using data from the central pharmacy computerized information system. Most patients admitted since the start of the pandemic were treated with low-molecular-weight heparin as standard prophylactic treatment to prevent the development of deep vein thrombosis and pulmonary embolism. However, after several international reports raised concerns about the potential risk of thromboembolism in COVID-19, local protocols recommended the use of intermediate and full-dose anticoagulation depending of the risk profile of the individual patient being considered. The choice of anticoagulation regimens ultimately relied on the criteria of each attending physician. All data were reviewed by the investigators on a case-by-case basis. Any disagreements regarding data classification were reviewed by the whole team, and a decision was finally made by consensus.

Statistical analysis

Categorical variables are shown as rates and percentages and continuous variables as mean (SD). The means for continuous variables were compared using independent group *t*-tests when the data were normally distributed, otherwise, the Mann–Whitney test was used. The normality of distributions was assessed using the Shapiro–Wilk test. Proportions for categorical variables were compared using the χ^2 test or the Fisher's exact test, as appropriate. Survival during follow-up was assessed using Kaplan–Meier analysis and, where appropriate, the log-rank test. Stepwise techniques were employed to develop multivariable predictive models using logistic regression and Cox proportional hazards models, selecting as candidate variables those who were statistically significant in the univariable analysis. Areas under the receiver operating characteristic curve (AUCs) and *c*-statistics as appropriate were used as a measure of the predictive accuracy of the scoring systems and predictive models. All data were analysed using the Stata v14.2 statistics package (StataCorp, College Station, TX, USA). A two-sided *P*-value <0.05 was considered statistically significant for all analyses.

Results

During the study period, 5556 patients with clinical suspicion of COVID-19 attended the Emergency Department of our tertiary care centre and were screened for participation in the present study (Figure 1). Of these, 3042 patients (mean age 62.3 ± 20.3 years, 54.9% male) with confirmed SARS-CoV-2 infection fulfilled all the selection criteria and were ultimately included in the present analysis.

Baseline characteristics and follow-up outcomes are shown in Table 1. Median time from the onset of symptoms to diagnosis was 6 (3–9) days, and the median length of follow-up was 59 (50–66) days. Of the 3042 patients, 2173 (71.4%) required hospital ward admission during the study period, the leading reason being radiological

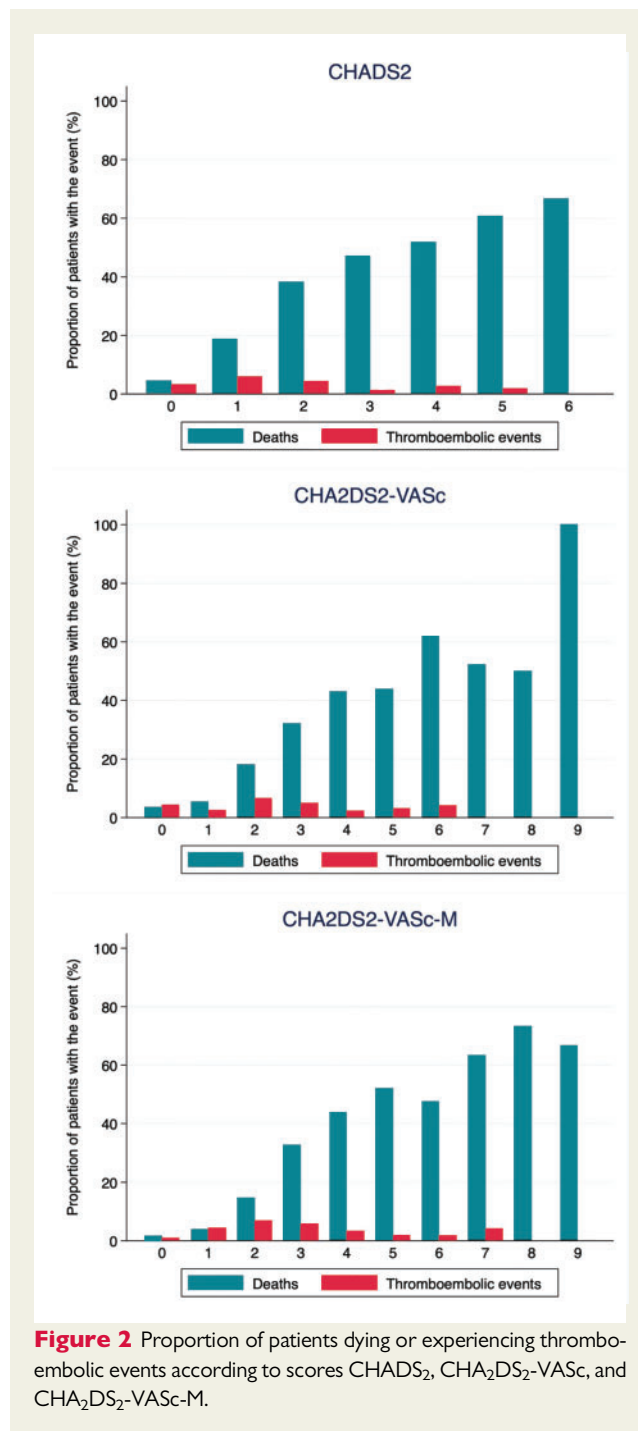


Figure 2 Proportion of patients dying or experiencing thromboembolic events according to scores CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M.

pneumonia at the initial chest radiography (1846 patients, 1413 of them with bilateral infiltrates). The included patients had a significant burden of baseline CV risk factors: 1309 (43.0%) had hypertension, 556 (18.3%) diabetes, 1090 (35.8%) dyslipidaemia, and 298 (9.8%) were active smokers. Many also had prior AF (249, 8.1%), coronary heart disease (196, 6.4%), and heart failure (150, 4.9%). Baseline CV treatments and COVID-19-related medications initiated after diagnosis are also shown in Table 1. Detailed data regarding anticoagulation prescriptions in hospitalized patients are shown in Supplementary material online, Table S1 and Figures S1–S3. Among the whole study

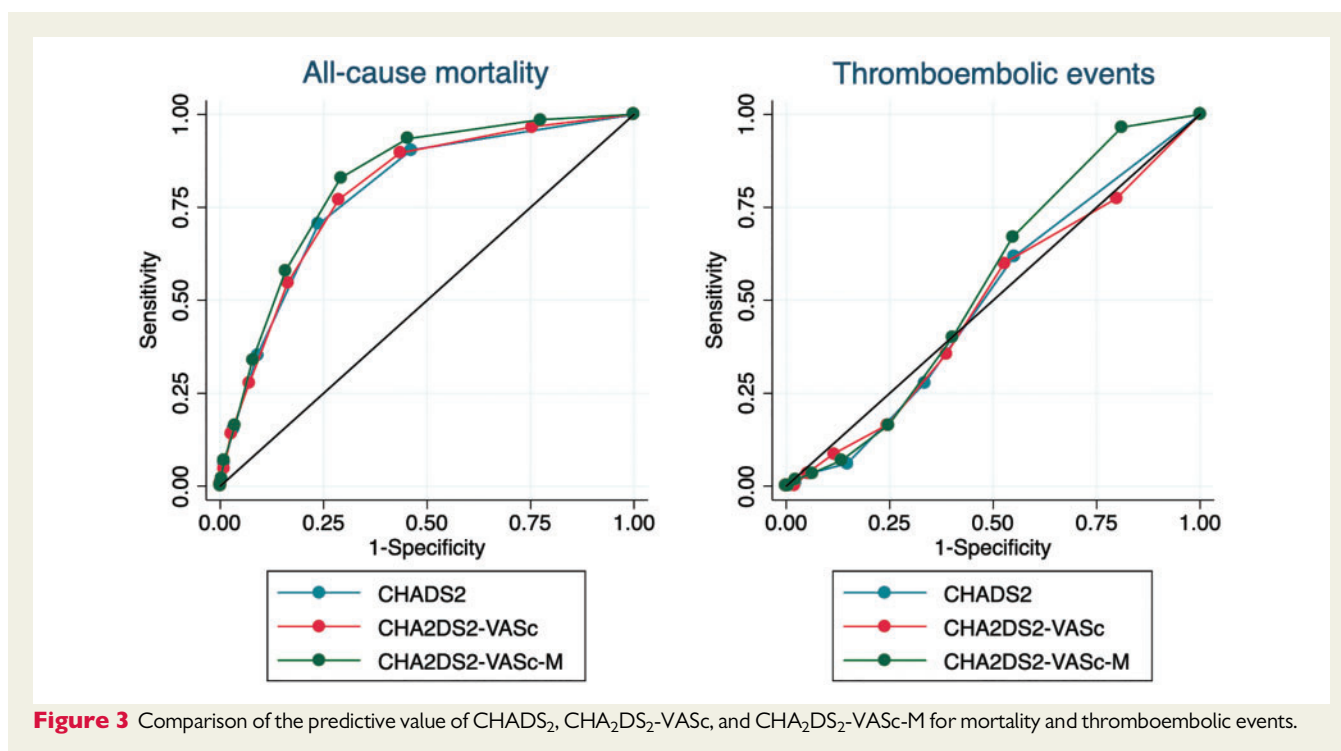


Figure 3 Comparison of the predictive value of CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M for mortality and thromboembolic events.

population, 115 (3.8%) presented a definite thrombotic event, 21 (0.7%) fulfilled criteria for severe bleeding, and 171 (5.6%) required mechanical ventilation during hospital admission. Overall, 626 patients (20.6%) died during the study period.

Patient characteristics and thromboembolic events

During follow-up, 115 patients (3.8%) presented with a definite thrombotic event, including 75 (2.5%) with pulmonary embolism, 17 (0.6%) with deep vein thrombosis, 5 (0.2%) with acute coronary syndrome, 18 (0.6%) with TIA/stroke, and 11 (0.4%) with peripheral artery events (Table 1).

These patients were significantly older, more frequently male and had a longer time from symptom onset to diagnosis. Notably, respiratory distress at admission was more prevalent in patients with thromboembolic complications, showing lower SatO₂ and more extensive radiological infiltrates. Furthermore, they had higher levels of biomarkers such as NT-proBNP and D-dimer. Except for lopinavir/ritonavir, specific COVID-19 treatment was more frequently used among patients with thromboembolic episodes, who also had more prolonged hospital admissions, more arrhythmia episodes, increased admission to critical care for mechanical ventilation and higher mortality. Multivariate analysis showed that prolonged hospitalization, elevated levels of D-dimer and NT-proBNP, critical care admission for mechanical ventilation, and use of tocilizumab were independent predictors of thromboembolic events (Supplementary material online, Table S2), with a c-statistic of 0.903.

Patient characteristics and mortality

Patients dying during the study period had a poorer baseline clinical profile compared to surviving patients (Table 2): they were older,

predominantly male, and showed a significantly higher prevalence of cardiovascular risk factors and CV disease. Cerebrovascular disease, peripheral artery disease, and other comorbidities, as well as common CV drugs, were significantly more prevalent among non-survivors. All COVID-19 treatments except lopinavir/ritonavir were more frequently used among these patients.

A multivariable predictive model of death during follow-up using stepwise regression techniques showed that age, male sex, peripheral artery disease, prior TIA/stroke, history of atrial flutter, time from symptoms to diagnosis, SatO₂ at admission, need for supplementary O₂ at admission, elevated levels of D-dimer and NT-proBNP, corticosteroids, and mechanical ventilation were independently associated with poorer outcomes, while hydroxychloroquine was associated with lower mortality (Supplementary material online, Table S3), the C-index for the model being 0.870.

Relationship between cardiovascular risk scores, thromboembolic events, and mortality

An increasing incidence of thromboembolic events was not seen with higher CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M ($P = 0.342$, $P = 0.464$, and $P = 0.618$ for trend, respectively). As shown in Figure 2 and Supplementary material online, Table S4, mortality during follow-up was higher with increasing score values of CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M ($P < 0.001$ for trend).

The three scores showed poor predictive value for thromboembolic events (Figure 3, right panel): AUC 0.497 (0.452–0.542), 0.490 (0.440–0.541), and 0.541 (0.501–0.581), respectively. On the other hand, the AUC for CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M and mortality was 0.788 (0.770–0.807), 0.794 (0.775–0.812), and 0.820 (0.803–0.836), respectively (Figure 3, left panel). No significant

differences were observed between CHADS₂ and CHA₂DS₂-VASc ($P=0.216$). By putting extra weight on male sex, the CHA₂DS₂-VASc-M showed the best predictive value compared with CHADS₂ ($P<0.001$) and CHA₂DS₂-VASc ($P<0.001$).

Figure 4 shows the Kaplan–Meier survival curves stratified by the categorization of CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M. Mortality was significantly increased in patients with higher score points ($P<0.001$ by the log-rank test in the three cases).

Causes of death and laboratory results

The different causes of death were stratified according to the categories of each scoring system (Table 3). The leading cause of death among all patients was respiratory failure non-related to pulmonary embolism (534, 87.8%). This specific cause of death increased with ascending CHA₂DS₂-VASc and CHA₂DS₂-VASc-M scores, while pulmonary embolism did not show any trend across the three scoring systems.

Finally, higher CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M scores were significantly related with median laboratory results during hospital admission (Table 4) regarding coagulation (lower prothrombin activity and higher D-dimer), inflammatory (higher C-reactive protein and fibrinogen, lower lymphocytes) and cardiac biomarkers (higher NT-proBNP and hs-troponin I).

Discussion

The CHADS₂ and CHA₂DS₂-VASc scores are two systems widely used to stratify thromboembolic risk in AF patients.⁴ In addition, they also predict all-cause mortality among a wide spectrum of cardiovascular diseases without concurrent AF, including pulmonary embolism.^{5,8} Both scores are based on age, common cardiovascular risk factors, and underlying cardiovascular disease. All these factors have been individually associated with poorer outcomes and increased mortality in COVID-19 patients.⁹ Additionally, a prothrombotic status with frequent thromboembolic complications has been speculated in COVID-19.¹⁰ Development of coagulopathy in severely ill SARS-CoV-2 patients has also been suggested by other authors¹¹ and may be one of the determinants of the clinical course of the disease.

Therefore, our initial hypothesis was that CHADS₂ and CHA₂DS₂-VASc scores would estimate the thromboembolic and mortality risks in COVID-19 patients with higher predictive value than their individual components. Besides, we postulated that a modified CHA₂DS₂-VASc score (the 'CHA₂DS₂-VASc-M score'), in which 1 point is given to male patients instead of female patients, would further enhance the predictive value of this score given the worse prognosis of COVID-19 of male sex in previous research.

Thromboembolic risk and cardiovascular scores

The risk assessment of thromboembolic events of the 3 scores was generally poor and close to the AUC 0.5 threshold in the ROC analysis. This finding supports mechanisms other than those involved in AF for thrombus formation and embolization. Thrombotic phenomena in COVID-19 may be better reflected by the distinct patterns of endotheliitis, local thrombosis, and angiogenesis, reflecting thrombo-

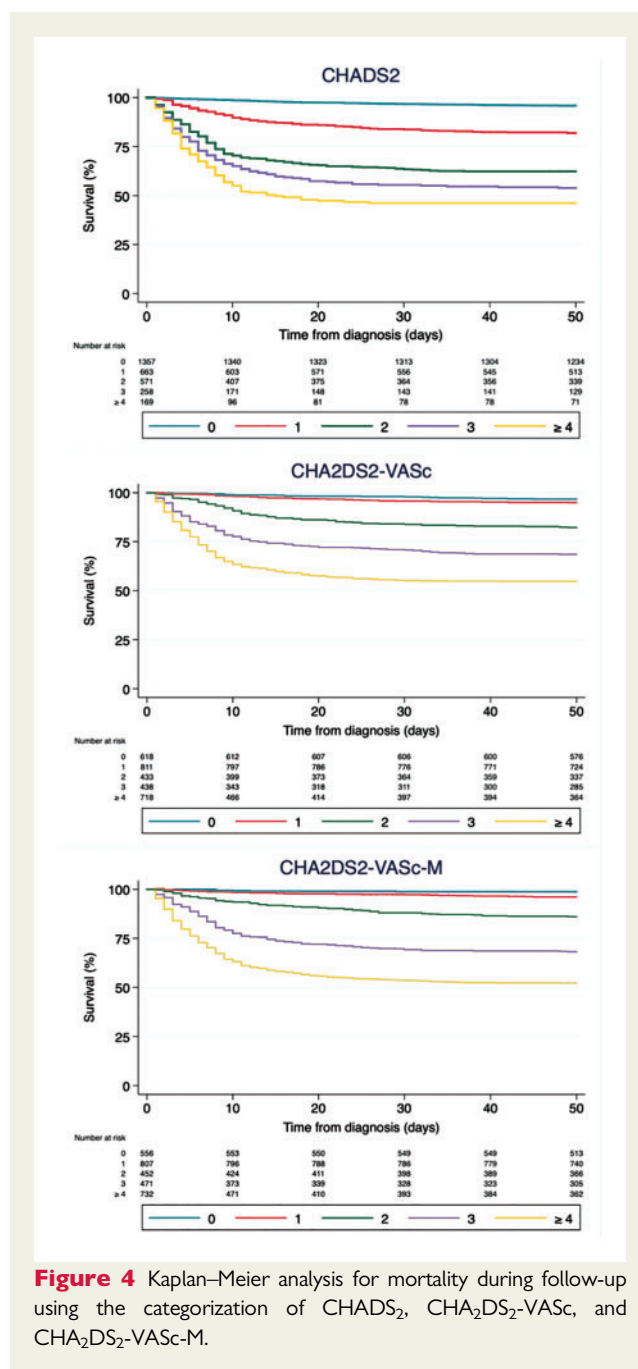


Figure 4 Kaplan–Meier analysis for mortality during follow-up using the categorization of CHADS₂, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M.

inflammation or immunothrombosis.¹² These presentations greatly differ from classical atherothrombotic or thromboembolic events, and there is the hypothesis that the deranged balance in the prothrombotic/antithrombotic properties of the endothelium may lead to thrombosis in situ in the pulmonary vessels and elsewhere.¹³

Mortality risk and cardiovascular scores

Our study illustrates that higher CHADS₂ and CHA₂DS₂-VASc predict higher mortality in COVID-19. Not surprisingly, the CHA₂DS₂-VASc-M showed an even better predictive value compared with the former scores, although statistical differences were small and may lack clinical relevance. A simple categorization of the three scores

Table 3 Causes of death

	Respiratory failure (non-PE) (n = 534)	Pulmonary embolism (n = 10)	Sudden death (n = 11)	Other (n = 53)
CHADS ₂				
0	46 (8.6%)	5 (50.0%)	0 (0.0%)	8 (15.1%)
1	104 (19.5%)	3 (30.0%)	3 (27.3%)	14 (26.4%)
2	195 (36.5%)	2 (20.0%)	5 (45.5%)	14 (26.4%)
3	108 (26.2%)	0 (0.0%)	2 (18.2%)	8 (19.1%)
≥4	81 (15.2%)	0 (0.0%)	1 (9.1%)	9 (17.0%)
CHA ₂ DS ₂ -VASc				
0	16 (3.0%)	2 (20.0%)	0 (0.0%)	3 (5.7%)
1	30 (5.6%)	3 (30.0%)	2 (18.2%)	7 (13.2%)
2	66 (12.4%)	1 (10.0%)	1 (9.1%)	9 (17.0%)
3	124 (23.2%)	3 (30.0%)	2 (18.2%)	11 (20.8%)
≥4	298 (55.8%)	1 (10.0%)	6 (54.6%)	23 (43.4%)
CHA ₂ DS ₂ -VASc-M				
0	7 (1.3%)	2 (20.0%)	0 (0.0%)	0 (0.0%)
1	25 (4.7%)	2 (20.0%)	0 (0.0%)	5 (9.4%)
2	49 (9.2%)	3 (30.0%)	2 (18.2%)	10 (18.9%)
3	137 (25.7%)	2 (20.0%)	3 (27.3%)	12 (22.6%)
≥4	316 (59.2%)	1 (10.0%)	6 (54.6%)	26 (49.1%)

Unexplained sudden death was defined according to standard definitions but adapted to the COVID-19 pandemic as a non-traumatic, unexpected fatal event occurring within 1 h of the onset of new symptoms in a subject without any acute diseases other than COVID-19 and a proven cause. If death was not witnessed, the definition applied when the victim was found death, have had no new symptoms or respiratory deterioration 24 h before the event and had no apparent cause for it. PE, pulmonary embolism.

was found to be highly significantly associated with survival as assessed by Kaplan-Meier analysis and the log-rank test. Notably, the excess mortality seen among patients with higher score points was not due to thromboembolic events but to progressive respiratory failure in the context of COVID-19 disease, apparently unrelated to pulmonary embolism (Table 3). Indeed, the use of full anticoagulation tended to increase with ascending scores of CHADS, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M (Supplementary material online, Table S1 and Figures S1–S3). Therefore, poorer outcomes in patients with higher scores were not related to inappropriately low rates of anticoagulation use.

Prognosis prediction in COVID-19

The COVID-19 pandemic has caused severe shortages and overwhelmed health care infrastructures all around the world. In this context, allocating medical resources may become a major problem and hospitals may be forced to develop triage policies and protocols, not always supported by clinical evidence. Patients with COVID-19 may deteriorate quickly, developing respiratory failure and requiring non-invasive and invasive mechanical ventilation. Delays in providing orotracheal intubation and admission to an intensive care unit may result in preventable deaths. On the other hand, uncertainties regarding the prognosis of an individual patient at first medical contact may in some cases unnecessarily increase the demand of medical resources including radiological tests and hospital admissions. Therefore, all efforts should be made to improve risk stratification and to provide clinicians with accessible tools to easily predict adverse outcomes.

Thus, prognostication in COVID-19 has been the subject of a large number of recent investigations.⁶ However, significant methodological limitations in the derivation and validation of predictive models have been pointed and after systematic evaluation, no single prognostic model has showed incremental value for risk stratification over several individual predictors. In addition, most of these models include biomarker levels or radiological data from computed tomography which make them complex and limit their applicability for initial prognostic stratification.

CHADS, CHA₂DS₂-VASc, and CHA₂DS₂-VASc-M are simple clinical risk scores that may be immediately calculated during the first medical contact. Its use, in combination with a comprehensive clinical evaluation, may improve risk assessment and allow attending physicians to prioritize resources and maximize clinical benefit (i.e. reducing hospital admissions for clinical observation in patients at very low risk of adverse events may avoid shortages and facilitate that key resources, such as intermediate-care areas, CT scans and ultimately healthcare workers are available for those patients that are in real need for them).

Cardiovascular scores and laboratory tests

Higher CV score points were associated with abnormal values of coagulation parameters (prothrombin activity and D-dimer) in our study. However, they were also associated with profound and progressive alterations of inflammatory and cardiac biomarkers. Shi et al.¹⁴ demonstrated that patients with cardiac injury defined as blood levels of cardiac biomarkers (hs-TnI) above the 99th-percentile upper

Table 4 Median analytical determinations of key parameters according to each score category

	Prothrombin activity	D-dimer	CRP	Fibrinogen	Lymphocytes	NT-proBNP	hs-Troponin I
CHADS₂							
0	91 (78–101)	680 (400–1750)	66.5 (17.6–168.4)	740 (517–1015)	950 (640–1390)	371.5 (68.5–1852.5)	3.2 (2.5–10.6)
1	87 (72–97)	1180.0 (636.0–5280.0)	121.5 (57.8–216.7)	878 (652–1170)	750 (480–1060)	800.5 (195.0–26.2)	9 (4.1–54.1)
2	81 (65–93)	1600.0 (767.0–4210.0)	139.9 (63.4–221.0)	855 (641–1125)	690 (480–990)	1544.0 (412.0–7133.0)	13.2 (5.2–53.5)
3	81 (63–93)	1422.0 (777.0–4166.0)	119.7 (68.6–190.6)	793 (623–1048)	650 (460–920)	1671.0 (580.0–5855.0)	15.5 (8.3–55.5)
≥4	77 (49–91)	1378.0 (786.5–3803.5)	134.9 (60.1–223.2)	842 (600–1135)	620 (430–890)	4622.0 (1762.0–9422.0)	33.2 (12.3–141.5)
CHA₂DS₂-VASc							
0	87 (76–97)	700.0 (380.0–1948.0)	77.8 (21.5–184.5)	807 (550–1134)	930 (630–1370)	188.5 (77.0–1514.0)	3.5 (2.5–10.7)
1	94 (81–104)	701.0 (414.0–1650.0)	65.5 (17.0–167.6)	734 (519–984)	935 (640–1379)	428.0 (53.0–2127.0)	3.9 (2.5–17.2)
2	87 (69–97)	1169.0 (589.5–5145.0)	125.4 (59.0–223.0)	908 (676–1154)	750 (490–1050)	693.0 (192.0–2475.0)	7.8 (3.4–39.4)
3	83 (66–95)	1710.5 (771.0–6656.0)	130.9 (64.7–217.0)	860 (652–1150)	640 (450–990)	1048.0 (389.0–3651.0)	13.1 (5.3–57.5)
≥4	81 (63–94)	1397 (778–3775)	124.8 (58.7–207.4)	803 (604–1065)	660 (460–940)	3130.5 (748.5–8177.5)	18.4 (7.2–78.0)
CHA₂DS₂-VASc-M							
0	98 (87–106)	548.0 (370.5–954.5)	36.5 (9.7–103.9)	633 (456–842)	1085 (790–1560)	54.0 (35.0–586.0)	2.5 (2.5–4.5)
1	89 (77–99)	738.0 (410.0–2216.0)	77.8 (25.3–184.2)	795 (558–1112)	910 (640–1295)	317.5 (84.0–1613.0)	3.9 (2.5–11.5)
2	87 (72–97)	1187.0 (618.0–6656.0)	126.2 (51.8–217.2)	875 (652–1188)	720 (470–1050)	778.0 (231.0–2385.0)	8.3 (3.7–53.5)
3	83 (67–94)	1418 (753.5–4676.0)	144.9 (65.6–221.0)	878 (647–1126)	710 (480–990)	1086.0 (351.0–5404.0)	11.7 (4.6–56.0)
≥4	78 (61–91)	1601.5 (801.5–4289.0)	134.8 (71.2–219.6)	849 (641–1134)	615 (430–900)	2535.5 (699.5–7305.0)	20.4 (9.0–78.8)

reference limit showed an independent relationship with higher mortality after adjusting for a large number of potential confounders. Indeed, a large recent cohort study including 2736 hospitalized patients illustrated that troponin elevation in COVID-19 is prevalent and associated with worse outcomes.¹⁵ Moreover, recent studies using cardiac magnetic resonance¹⁶ have reported myocardial abnormalities (including abnormal T1, T2, and late gadolinium enhancement) in a large proportion of patients recovered from COVID-19. These findings may be related to different complications associated with SARS-CoV-2 infection, such as myocarditis; takotsubo syndrome, and acute coronary syndromes.¹⁷ On the other hand, COVID-19 has been considered as a hyperinflammatory state¹⁸ and the potential role assigned to the associated 'cytokine storm' has led to the prescription of inflammatory modulators such as tocilizumab and corticosteroids.¹⁹ The so-called lung-restricted vascular immunopathology associated with COVID-19²⁰ has been described as a diffuse pulmonary intravascular coagulopathy associated with increased D-dimer and elevated cardiac enzymes and may be related to the reported pathological findings.¹² Immunological changes found in COVID-19, that share characteristics with the macrophage activation syndrome, may be reflected by the abnormalities in inflammatory biomarkers observed in our patients. This observation may lead to the hypothesis that higher CHADS₂, CHA₂DS₂-VAsC, and CHA₂DS₂-VAsC-M may in fact reflect a significant pro-inflammatory state in the context of COVID-19 disease, leading to more severe pulmonary intravascular coagulopathy and higher mortality during follow-up.

Limitations

Some limitations should be considered in our study. First, our population is older and presented significantly more comorbidities than other cohorts reported in the literature. Healthcare recommendations in Spain during the lockdown period made that patients with milder COVID-19 symptoms were attended by their primary care physicians and not referred to large hospitals. As a result, most of our patients presented with pneumonia, required hospital ward admission and had high mortality risk at follow-up. They should not be viewed as representative of the whole COVID-19 population. Secondly, prioritization of hospital resources and isolation protocols to avoid the spread of the disease may have led to restricted computed tomography for pulmonary embolism detection in some patients. This may have resulted in underestimation of thrombotic events during follow-up. Ongoing post-COVID surveillance programs include comprehensive imaging protocols that may improve the detection of cases that may have been missed during the index admission.

Conclusions

CHADS₂, CHA₂DS₂-VAsC, and the modified CHA₂DS₂-VAsC-M do not predict the incidence of thromboembolic events in COVID-19 patients. However, they do predict mortality risk during follow-up. Therefore, implementation of these simple, commonly used risk scores may facilitate prognostic stratification at the initial medical contact without additional laboratory or hospital tests.

Supplementary material

Supplementary material is available at *Europace* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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