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Mortality prediction using a modified $R_2CHA_2DS_2$-VASc score among hospitalized COVID-19 patients

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Abstract

The CHA_2DS_2-VASc score incorporates several comorbidities which have prognostic implications in COVID-19. We assessed whether a modified score (M-$R_2CHA_2DS_2$-VASc), which includes pre-admission kidney function and male sex, could be used to classify mortality risk among people hospitalized with COVID-19. This retrospective study included adults admitted for COVID-19 between March and December 2020. Pre-admission glomerular filtration rate (GFR) was calculated based on serum creatinine and used for scoring M-$R_2CHA_2DS_2$-VASc. Participants were categorized according to the M-$R_2CHA_2DS_2$-VASc categories as 0–1 (low), 2–3 (intermediate), or ≥ 4 (high), and according to initial COVID-19 severity score. The primary outcome was 30-day mortality rates. Secondary outcomes were mortality rates over time, and rates of mechanical ventilation, hemodynamic support, and renal replacement therapy. Eight hundred hospitalizations met the study criteria. Participants were 55% males, average age was 65.2 ± 17 years. There were similar proportions of subjects across the M-$R_2CHA_2DS_2$-VASc categories. 30-day mortality was higher in those in higher M-$R_2CHA_2DS_2$-VASc category and with severe or critical COVID-19 at admission. Subjects in the low, intermediate, and high M-$R_2CHA_2DS_2$-VASc categories had 30-day mortality rates of 4.7%, 17% and 31%, respectively ($p < 0.001$). Higher category was also associated with increased need for mechanical ventilation and renal replacement therapy. All-cause 90-day mortality remained significantly associated with M-$R_2CHA_2DS_2$-VASc. The M-$R_2CHA_2DS_2$-VASc score is associated with 30-day mortality rates among patients hospitalized with COVID-19, and adds predictive value when combined with initial COVID-19 severity.

Keywords SARS-CoV-2 infection · COVID-19 · Mortality · Outcome · Kidney function · GFR

Introduction

From the early stages of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, it was evident that pre-existing medical conditions significantly affected disease outcomes [1, 2]. In addition to increasing age and male sex, common cardiovascular comorbidities are associated with worse prognosis and mortality from coronavirus disease 2019 (COVID-19) [2–4].

The CHA_2DS_2-VASc score, which was originally developed to predict risk for stroke and thromboembolism among patients with atrial fibrillation [5], incorporates many of these risk factors, and thus, may predict outcomes among COVID-19 patients.

Since male sex is an important predictor of critical illness and mortality from COVID-19, a modified CHA_2DS_2-VASc score in which 1 point is given for male sex instead of female sex, has demonstrated better predictive value for COVID-19

The article belongs to COVID 19.

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mortality in a few studies [6–9]. Chronic kidney disease has also emerged as a major risk factor for death from COVID-19, with worse estimated glomerular filtration rates (eGFR) associated with higher mortality [10, 11]. Thus, a scoring system that includes baseline renal function as well as other common comorbidities may improve outcome prediction related to COVID-19.

The purpose of this study was to investigate whether the modified $R_2CHA_2DS_2$-VASc score (M-$R_2CHA_2DS_2$-VASc), which includes higher scores for worsening kidney function, can predict mortality in subjects hospitalized with COVID-19.

Methods

This was a retrospective, observational study. Results are reported according to the STROBE statement guidelines.

Participants

The study population included adults ≥ 18 years of age admitted with COVID-19 to Meir Medical Center in Israel from March 1, 2020 through December 31, 2020. The diagnosis of SARS-CoV-2 infection was ascertained by a positive real-time reverse transcriptase polymerase chain reaction (RT-PCR) result from nasopharyngeal swabs. A cycle threshold of 35 or less was considered positive. We included only the first admission for each participant and excluded readmissions. Additional exclusion criteria included cases with missing data, as well as patients after renal transplantation.

Variables

Clinical, laboratory and radiologic data were extracted from the participants' electronic medical records. The day of first positive swab for SARS-CoV-2 served as day 0 of illness.

Baseline clinical variables included age, sex, smoking history, comorbidities and regular medications. Variables related to COVID-19 included clinical findings at presentation (COVID-19 symptoms and vital signs); laboratory and radiological findings during admission and treatments given for COVID-19. Disease severity at admission was ranked according to National Institute of Health guidelines as asymptomatic, mild, moderate (with clinical or radiographic evidence of lower respiratory tract disease and oxygen saturation ≥ 94% while breathing room air), severe (saturation < 94%, respiratory rate > 30/min, infiltrates over 50% of lungs volume), or critical (requiring invasive or non-invasive ventilation, in shock, or with organ failure) [12].

Pre-admission glomerular filtration rate (GFR) was estimated using the Modified Diet in Renal Disease (MDRD) equation, which enables GFR estimation from serum creatinine [13]. Basic serum creatinine measurement during the 3-month period prior to admission was used to calculate eGFR.

M-$R_2CHA_2DS_2$-VASc score calculation

The modified $R_2CHA_2DS_2$-VASc score was calculated by assigning one point each for the presence of: congestive heart failure, hypertension, diabetes mellitus, vascular disease and age 65–74 years, and two points for age older than 75 years and history of stroke or transient ischemic attack. GFR above 60 ml/min was given 0 points, GFR 30–60 ml/min was given 1 point and GFR below 30 ml/min was given 2 points [14] (Table 1).

Since male sex is a risk factor for adverse COVID-19 outcomes, we used the modified $R_2CHA_2DS_2$-VASc calculator, in which 1 point was assigned to men.

Study groups

To compare outcomes according to M-$R_2CHA_2DS_2$-VASc, patients were categorized according to the M-$R_2CHA_2DS_2$-VASc score: 0–1 (low), 2–3 (intermediate), or ≥ 4 (high) (Table 1).

Outcome measures

The primary outcome was 30-day mortality rate since COVID-19 diagnosis, which was compared among study groups. Secondary outcomes were overall mortality rates during follow-up (mortality data were collected until March 2021), rates of mechanical ventilation, hemodynamic support, and renal replacement therapy.

Table 1 Calculations of the R_2-CHA_2DS_2-VASc score and categories

R_2-CHA_2DS_2-VASc score			Category	Total score
R_2	eGFR < 60 ml/min	1 point	Low	0–1
	eGFR < 30 ml/min	2 points	Intermediate	2–3
C	Congestive heart failure	1 point	High	≥ 4
H	Hypertension	1 point		
A_2	Age > 75 years	2 points		
D	Diabetes mellitus	1 point		
S_2	Previous stroke or TIA	2 points		
V	Vascular disease	1 point		
A	Age 65–74	1 point		
Sc	Sex category (male)	1 point		

Estimated glomerular filtration rate (eGFR) above 60 ml/min was given 0 points. eGFR was calculated for each patient using the MDRD formula

TIA transient ischemic attack

Statistical analysis

Descriptive statistics are presented as means, medians or percentages with standard deviations and range. Comparison of variables between two study groups was performed using *t* test, Mann–Whitney test, Fisher's exact test or chi-square test, according to the scale of the variable. Continuous variables were examined for normality (Shapiro–Wilk test) and data were analyzed accordingly. The *t* test or one-way ANOVA was applied for normally distributed variables and the Mann–Whitney or Kruskal–Wallis for non-parametric variables. A multivariate logistic regression model including all significant variables in the univariate analysis was applied to estimate odds ratios of mortality across different M-$R_2CHA_2DS_2$-VASc categories. Survival curves were obtained using the Kaplan–Meier method and compared using two-sided log rank statistics. We used receiver operating characteristic (ROC) curves and areas under the curves (AUC) to assess the predictability of the $R_2CHA_2DS_2$-VASc and M-$R_2CHA_2DS_2$-VASc scores. A P value < 0.05 was considered statistically significant. Data were analyzed using SPSS, Version 27 (IBM Corporation, Armonk, NY, USA).

Compliance with ethical standards

The study was approved by the Ethics Committee and Institutional Review Board of Meir Medical Center (application no. MMC-0016-21). The committee waived the requirement for informed consent due to the retrospective nature of the study. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Results

Clinical presentation

There were 969 hospitalizations for COVID-19 during the study period, 800 of which fulfilled the inclusion and exclusion criteria. Mean age of participants was 65.2 ± 17 years, 55.5% were men. The average follow-up period was 108 ± 84 days after admission. A total of 258 patients (32%) were categorized as low M-$R_2CHA_2DS_2$-VASc score, 265 (33%) as intermediate and 277 (35%) as high M-$R_2CHA_2DS_2$-VASc. As expected, those in a higher M-$R_2CH_A2DS_2$-VASc category were older, more often male, and had a higher prevalence of pre-existing cardiovascular comorbidities. The rate of malignancy, however, was similar between study groups. Baseline characteristics of participants are presented in Table 2.

COVID-19 severity at admission was available for 693/800 patients (87%). Overall, 289 (42%) were classified as having mild disease, 171 (25%) as moderate, 209 (30%) as severe, and 24 (3%) as critical COVID-19 disease at admission. The distribution of initial disease severity was similar across the three M-$R_2CHA_2DS_2$-VASc categories (Fig. 1, $p = 0.26$).

Higher M-$R_2CHA_2DS_2$-VASc group was associated with increased requirements for mechanical ventilation (14.8%, 13.2%, and 6.6%, $p = 0.008$) and renal replacement therapy (10.5%, 0.4%, and 0%, $p < 0.001$) in the high, intermediate, and low groups respectively, but not for vasopressor support (2.9%, 1.5% and 0.8%, respectively, $p = 0.165$).

Table 2 Baseline characteristics according to R_2-CHA_2DS_2-VASc categories

Characteristic	R_2-CHA_2DS_2-VASc Score category			*P* value
	Low (0–1)	Intermediate (2–3)	High (≥4)	
Number	258 (32.3%)	265 (33.1%)	277 (34.6%)	
Age, years	49.4 ± 14.2	68.8 ± 12.5	76.4 ± 11.3	< 0.001
BMI	30 ± 17.3	28.4 ± 6.2	28.4 ± 5.8	0.983
Male sex	94 (36.4%)	163(61.5%)	187 (67.5%)	< 0.001
Hypertension	14 (5.4%)	119 (44.9%)	234 (84.5%)	< 0.001
Current smoker	9 (3.5%)	19 (7.2%)	30 (10.8%)	< 0.001
Heart failure	1 (0.4%)	5 (1.9%)	39 (14.1%)	< 0.001
COPD	13 (5%)	19 (7.2%)	27 (9.7%)	0.113
Diabetes mellitus	11 (4.3%)	83 (31.3%)	172 (62.1%)	< 0.001
Previous stroke	0 (0%)	3 (1.1%)	63 (22.7%)	< 0.001
Chronic kidney disease	1 (0.4%)	16 (6%)	97 (35%)	< 0.001
Atrial fibrillation	6 (2.3%)	12 (4.5%)	44 (15.9%)	< 0.001
Ischemic heart disease	1 (0.4%)	10 (3.8%)	102 (36.8%)	< 0.001
Malignancy	3 (1.2%)	6 (2.3%)	7 (2.5%)	0.494

Values are presented as mean ± standard deviation or as absolute number (percentages)

BMI body mass index, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *AF* atrial fibrillation, *IHD* I

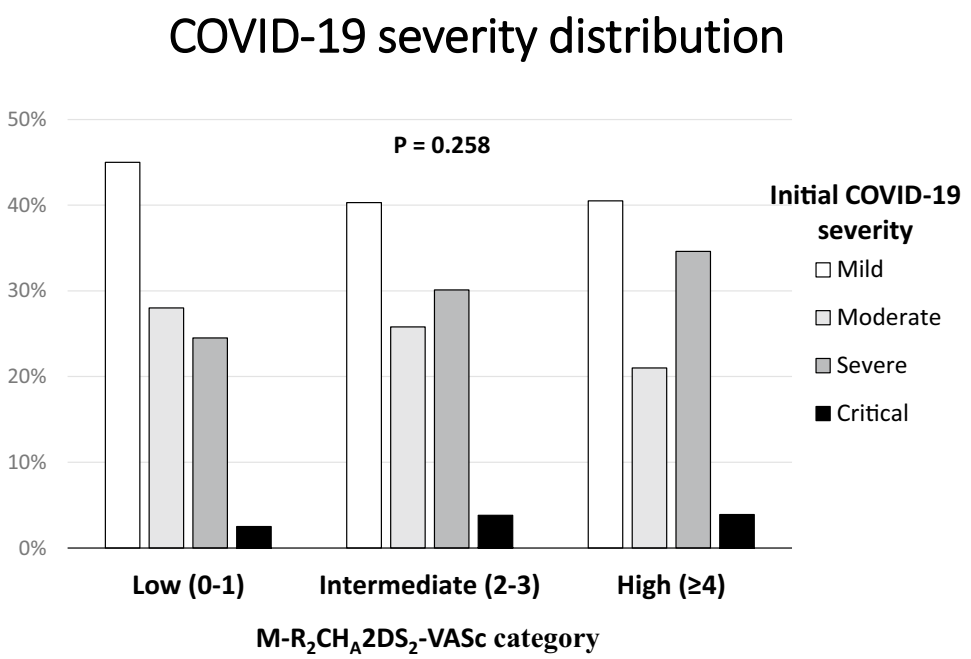

Fig. 1 COVID-19 severity at admission according to M-$R_2CHA_2DS_2$-VASc category. The distribution of initial disease severity (according to National Institute of Health guidelines) was similar across the different M-$R_2CHA_2DS_2$-VASc categories ($p = 0.258$)

Table 3 Odds ratios (OR) for 30-day mortality according to COVID-19 severity at hospital admission

COVID-19 severity	OR for mortality	*P* value
Mild (reference)	1	1
Moderate	0.83 (0.42–1.67)	0.6
Severe	5.43 (3.32–8.89)	< 0.0005
Critical	50.58 (16.07–159.19)	< 0.0005

Values are presented as OR (95% confidence interval)

Mortality

The overall 30-day mortality rate was 17.9%. Mortality was significantly higher among those in higher M-$R_2CHA_2DS_2$-VASc categories: 31% for high, 17% for intermediate, and 4.7% for low M-$R_2CHA_2DS_2$-VASc scores, respectively ($p < 0.001$). The odds ratios for a fatal outcome were 4.2 in the intermediate M-$R_2CHA_2DS_2$-VASc group and 9.2 for the high M-$R_2CHA_2DS_2$-VASc group, compared to the low M-$R_2CHA_2DS_2$-VASc group, which served as reference.

COVID-19 severity at presentation to the hospital was also associated with 30-day mortality. Mortality rates according to disease severity were 9%, 7.6%, 34.9% and 83.3% among the mild, moderate, severe, and critical COVID-19 groups, respectively ($p < 0.0001$). Odds ratio for mortality were higher among the severe and critical COVID-19 groups only, when compared to the mild disease severity group (Table 3).

Overall, the 30-day mortality rate for the mild and moderate COVID-19 groups combined was 8.5% (39/460). Within this group, a higher M-$R_2CHA_2DS_2$-VASc category was associated with increased mortality: odds ratios for a fatal outcome were 3.3 (95%CI 0.9–12.1, $p = 0.07$) for intermediate and 9.4 (95%CI 2.8–31.8, $p < 0.0001$) for high categories, when compared to the low category which served as reference. M-$R_2CHA_2DS_2$-VASc categorization retained its predictive value among patients admitted with severe COVID-19. 30-day mortality rates for the low, intermediate, and high categories among this group were 6.1%, 36.6%, and 49.4%, respectively ($p < 0.01$). However, for patients with critical COVID-19 at presentation, mortality rates were similar between different M-$R_2CHA_2DS_2$-VASc categories.

The combination of M-$R_2CHA_2DS_2$-VASc categories and COVID-19 severity categories was able to differentiate the mortality risk, increasing from 2.2% for the low M-$R_2CHA_2DS_2$-VASc/mild COVID-19 group to 100% for the high M-$R_2CHA_2DS_2$-VASc/critical COVID-19 group, $p < 0.01$ (Fig. 2).

The association between M-$R_2CHA_2DS_2$-VASc categories and overall survival remained significant for over 90 days after hospital admission, $p < 0.001$ (Fig. 3).

The predictive accuracy for 30-day mortality of the M-$R_2CHA_2DS_2$-VASc score was superior to the $R_2CHA_2DS_2$-VASc score (assigning 1 point to women and not men), ROC AUCs were 0.714 and 0.687, respectively, $p < 0.01$ (Fig. 4).

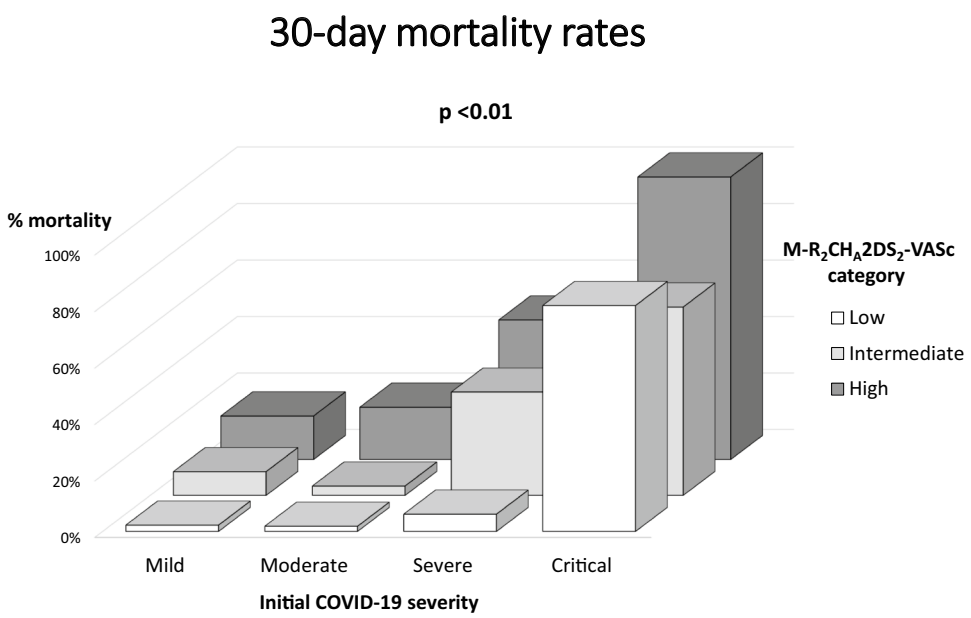

Fig. 2 30-day mortality rates according to M-$R_2CHA_2DS_2$-VASc category and COVID-19 severity. Mortality rates were dependent on both M-$R_2CHA_2DS_2$-VASc category and initial disease severity (according to National Institute of Health guidelines). Combining both scores added discriminative value for mortality prediction. Mortality rates were low for patients with mild–moderate COVID-19 and low M-$R_2CHA_2DS_2$-VASc category (2.2% and 1.8%, respectively); yet, rose to 100% for subjects with critical COVID-19 and high M-$R_2CHA_2DS_2$-VASc category, $p < 0.01$

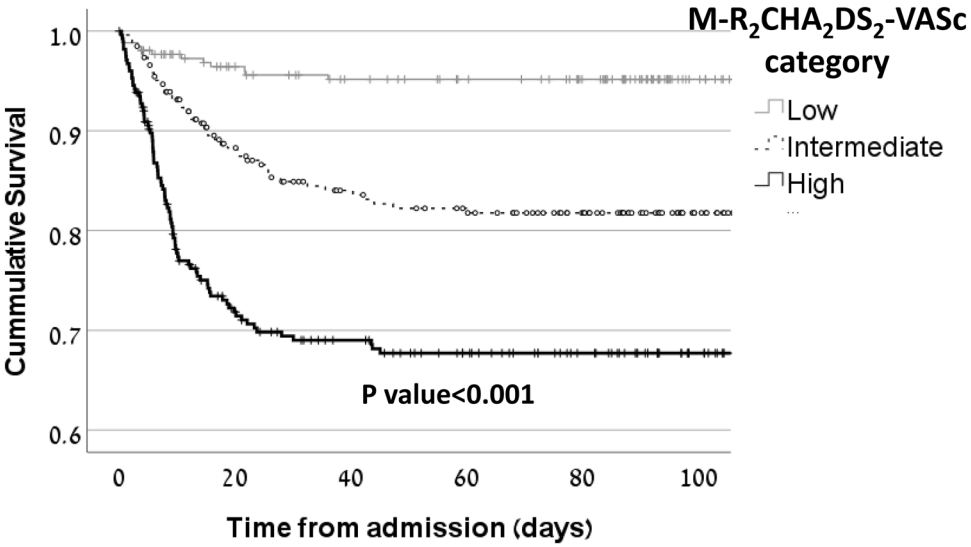

Fig. 3 Survival according to M-$R_2CHA_2DS_2$-VASc category. Survival curves using the Kaplan–Meier method were significantly different according to M-$R_2CHA_2DS_2$-VASc categories ($p < 0.001$)

Discussion

In the current study, the M-$R_2CHA_2DS_2$-VASc score was able to predict 30-day mortality rates among subjects hospitalized with COVID-19. Higher scores were associated with increased mortality.

The clinical spectrum of COVID-19 is wide, and ranges from asymptomatic cases to life-threatening disease with severe respiratory distress and multiorgan failure. Clinical deterioration usually begins a week after the onset of symptoms, so that the initial presentation may not reflect outcomes and prognosis [1]. Thus, an effective triage system which can allow appropriate allocation of medical resources is needed, especially when disease burden in the population is high.

An advantage of the M-$R_2CHA_2DS_2$-VASc score is that it incorporates several important comorbidities and risk factors into a simple calculation. We believe that it can be obtained easily and quickly among a multitude of healthcare settings, without additional resources. It was possible to retrospectively calculate it for all the participants in our study, and theoretically, it can be calculated automatically using electronic medical records systems.

Our results agree with previous reports of similar risk scores in COVID-19 patients, including the $CHADS_2$ score, the CHA_2DS_2-VASc score, and gender-modified versions of those scoring systems. In those studies, as in

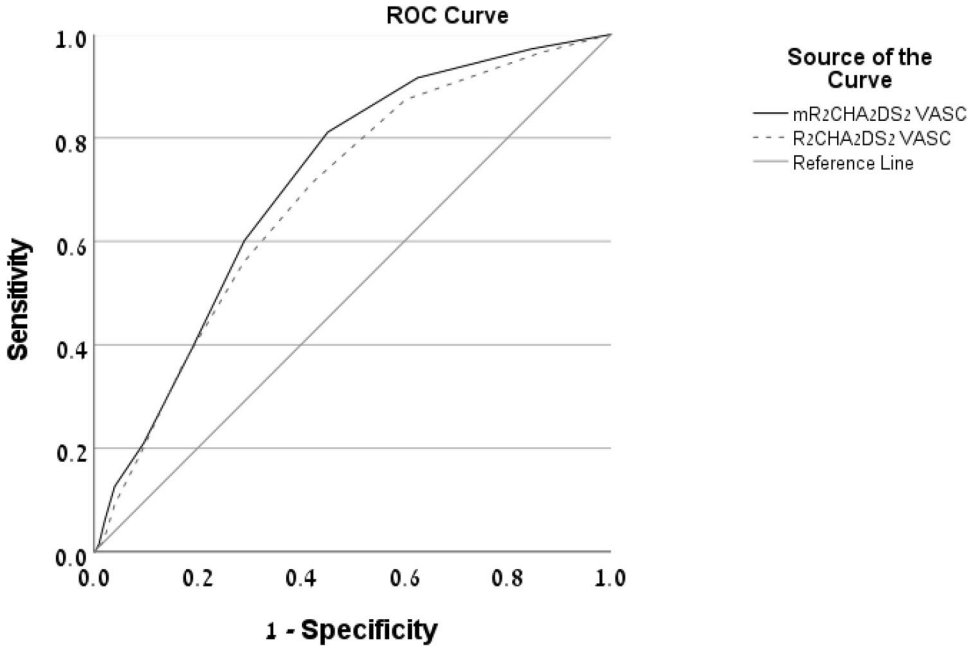

Fig. 4 Comparison of ROC curves. ROC curves for the M-$R_2CHA_2DS_2$-VASc and $R_2CHA_2DS_2$-VASc scores. AUC for M-$R_2CHA_2DS_2$-VASc was 0.714 and for $R_2CHA_2DS_2$-VASc 0.687. One point was assigned to men, instead of women, in the M-$R_2CHA_2DS_2$-VASc

ours, risk score categories were predictive of COVID-19 mortality [6–9]. A recently published study reported that an $R_2CHA_2DS_2$-VASc score had a better predictive value than other scores, including the CHA_2DS_2-VASc [15]. Our study, however, differs significantly from that report in several aspects. First, kidney function in the study by Katkat et al. was assessed based on in-hospital laboratory values, and not on pre-admission GFR. Second, the method of $R_2CHA_2DS_2$-VASc calculation was not reported, yet it did not include the modification according to gender employed in our study, or categorization into categories that can simplify use of the score. In addition, the sample size of the previous study was smaller (508 patients). Nevertheless, our results are in line with those of Katkat et al., which adds further support to their validity. However, we speculate that the addition of kidney failure as an important risk factor would make the M-$R_2CHA_2DS_2$-VASc more accurate and generalizable.

We use a different calculation for the M-$R_2CHA_2DS_2$-VASc than originally described for individuals with atrial fibrillation [16]. First, since male sex is associated with worse COVID-19 outcomes, we assigned 1 point for males instead of females. Second, we ranked kidney failure in three categories according to eGFR. Categories of CKD according to eGFR were significantly associated with mortality in a study based on a huge database of over 17 million COVID-19 patients. In that study, mortality risk was increased in those with eGFR of 30–60 ml/min/1.73m^2 and even more with eGFR < 30 ml/min/1.73m^2 [11]. Accordingly, we used those eGFR cutoff levels for the M-$R_2CHA_2DS_2$-VASc in our study. We categorized patients into three groups according to the score, as previously described [14].

Limitations of the current study include its retrospective and single center nature, and modest sample size. While M-$R_2CHA_2DS_2$-VASc scores were based on pre-admission data, the study only assessed inpatients, and the results cannot be generalized to ambulatory settings. The impact of vaccination on disease outcomes in cases of breakthrough COVID-19 has not been thoroughly investigated; thus, we cannot conclude whether our results are relevant to vaccinated patients with COVID-19. However, we believe that this supports our results, as the absence of previous vaccination may better reflect the natural history of COVID-19.

Despite these limitations, we believe that categorizing patients hospitalized with COVID-19 according to M-$R_2CHA_2DS_2$-VASc may have prognostic value for those patients, as it is easily obtainable and adds discriminative information to the COVID-19 severity score.

The M-$R_2CHA_2DS_2$-VASc added important predictive value when combined with the COVID-19 severity categorization, especially for patients with mild or moderate COVID-19 at admission. A higher M-$R_2CHA_2DS_2$-VASc category identified at-risk patients who are prone to deteriorate and have increased mortality. Thus, combining initial COVID-19 severity category with the M-$R_2CHA_2DS_2$-VASc score could help triage patients who require careful monitoring and who might benefit from specific treatments. The fact that M-$R_2CHA_2DS_2$-VASc categories were not predictive of 30-day mortality among patients with critical COVID-19 at admission is probably related to the small number of patients in this group.

Several prediction models for COVID-19 outcomes have been developed. Some are based on disease presentation, such as measurements of oxygen saturation and respiratory

rate at admission [17, 18], or laboratory and imaging studies. Others include baseline patient characteristics and comorbidities. One of the most well-validated models, the ISARIC 4C Mortality Score, shares the comorbidities included in the M-$R_2CHA_2DS_2$-VASc, with the addition of disease severity parameters [19]. However, it has not gained wide clinical acceptance, possibly because of its relative complexity. COVID-19 severity categories are very commonly used worldwide, to assess suitability for specific medications. We think that adding the M-$R_2CHA_2DS_2$-VASc score can easily provide significant predictive data and aid clinicians treating patients with COVID-19.

Author contributions All authors had full access to the data and participated in writing the manuscript.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights statement and Informed consent The study was approved by the Ethics Committee and Institutional Review Board of Meir Medical Center (application no. MMC-0016-21). The committee waived the requirement for informed consent due to the retrospective nature of the study. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

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