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Prognostic value of semi-quantitative CT-based score integrated with cardiovascular risk factors during the first peak of the COVID-19 pandemic:

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A new score to predict poor outcome

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ABSTRACT

Purpose: Predicting the clinical course of COVID-19 pneumonia is of high clinical importance and may change treatment strategies. This study aimed to compare the semi-quantitative CT score (radiological score), mCHA2DS2-VASc score (clinical score), and *R-mCHA2DS2-VASc* score (clinical and radiological score) to predict the risk of ICU admission and mortality in COVID 19 pneumonia.

Methods: This study retrospectively evaluated 901 COVID-19 pneumonia cases with positive PCR results. The mCHA2DS2-VASc score was calculated based on clinical risk factors. CT images were evaluated, and the semiquantitative CT scores were obtained. A new scoring method (*R-mCHA2DS2-VASc* score) was developed by combining these scores. The performance of the mCHA2DS2-VASc score, semi-quantitative CT score, and a combination of these scores (*R-mCHA2DS2-VASc* score) was evaluated using ROC analysis.

Results: The ROC curves of the semi-quantitative CT, mCHA2DS2-VASc, and *R-mCHA2DS2-VASc* scores were examined. The semi-quantitative CT, mCHA₂DS₂-VASc, and *R-mCHA₂DS₂-VASc* scores were significant in predicting intensive care unit (ICU) admission and mortality (p *<* 0.001). The *R-mCHA2DS2-VASc* score performed best in predicting a severe clinical course, and the cut-off value of 8 for the *R-mCHA2DS2-VASc* score had 83.9% sensitivity and 91.6% specificity for mortality.

Conclusions: The *R-mCHA2DS2-VASc* score includes both clinical and radiological parameters. It is a feasible scoring method for predicting a severe clinical course at an early stage with high sensitivity and specificity values. However, prospective studies with larger sample sizes are warranted.

1. Introduction

Coronavirus disease 2019 (COVID-19) emerged in Hubei city of Wuhan province in China in December 2019 and was declared a pandemic by the World Health Organization (WHO) on March 11, 2020. As of December 21, 2021, the WHO had reported *>*275 million confirmed cases and *>*5.3 million deaths related to COVID-19 worldwide [1].

Since the COVID-19 pandemic continues to cause significant strain

on the health care system, the importance of patient stratification and risk prediction for unfavorable outcomes has been emphasized its importance. Regarding its high-sensitivity chest CT has been widely used for diagnosis, triage, and follow-up $[2-4]$. Previous studies have demonstrated that the extent of lung involvement on chest CT represents an important prognostic factor, and semi-quantitative scoring systems based on the measurement of the volume of the lung segment affected were developed to predict the clinical severity [5,6].

COVID-19 is also associated with an increased risk of

Abbreviations: COVID-19, Coronavirus Disease 2019; CT, Computed Tomography; ICU, Intensive Care Unit; RT-PCR, Real-Time Polymerase Chain Reaction; WHO, World Health Organization; HT, Hypertension; DM, Diabetes Mellitus; CHF, Congestive Heart Failure; CKD, Chronic Kidney Disease; CAD, Coronary Artery Disease.

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thromboembolic events, which causes significant mortality and morbidity [7–9]. The incidence of thrombotic complications in COVID-19 patients admitted to the intensive care unit ranges from 31 to 34% [10,11]. Several mechanisms have been suggested as causes of the thrombotic complications of COVID-19; however, the thromboinflammatory state which causes microvascular endothelial damage is considered to be the main cause [12,13]. Considering the high risk of thromboembolic events in COVID-19 patients, the $CHA₂DS₂$ -VASc score (C: Congestive heart failure, H: Hypertension, A: Age \geq 75 years, D: Diabetes Mellitus, S: Stroke, V: Vascular disease, A: Age 65–74 years, Sc: Sex category, female) was proposed, and the results showed that a higher CHA₂DAS₂-VASc score was associated with higher mortality [14]. This score has been widely used to estimate the risk of stroke in cardiovascular diseases, particularly in atrial fibrillation, and has been accepted as a sound clinical risk score for the thrombotic process [15].

In addition to chest imaging, clinical and laboratory findings are essential in the clinical decision-making process and should be taken into consideration for accurate prognosis estimation. Older age, male sex, and comorbidities are potential risk factors for poor outcomes [16–18]. Various risk stratification models have been constructed over

the course of the pandemic based on either clinical, physiological, or imaging data. Studies have shown that comprehensive evaluation of radiological data integrated with clinical and laboratory parameters significantly increases the power of the prediction model [19–22]. However, no model is routinely used in clinical practice despite the development of these predictive models [23]. To close this gap in the literature, we investigated whether integrating this clinical score, which includes the prognostic risk factors for COVID-19 and estimates the thromboembolic event risk with the radiological semi-quantitative CT severity score, could predict an unfavorable clinical course.

In this context, the main purpose of this retrospective study was to evaluate the performance of a semi-quantitative CT-based score integrated with cardiovascular risk factors in predicting mortality and ICU admission in patients with COVID-19.

2. Materials and methods

2.1. Patients selection

In this study, the CT images of 3556 patients admitted to the hospital

Fig. 1. Flowchart of inclusion of the patients.

with suspected COVID 19 between March 1 and December 1, 2020, during the first peak of the pandemic, were scanned. The exclusion criteria included: (1) patients with negative RT-PCR test results; (2) patients without lung parenchymal involvement; (3) patients with suboptimal quality examination due to motion artifact; (4) patients with a history of lung mass or previous lobectomy; (5) patients with systemic diseases with parenchymal fibrosis (such as usual interstitial pneumonia, hypersensitivity pneumonia); (6) patients under chemotherapy and/or radiotherapy; and (7) patients under 18 years of age. A total of 901 patients were included in this study. (Fig. 1)

This retrospective study was approved by the Institutional Ethics Committee (IRB approval number: 2; date: 4/1/2021).

2.2. Data collection and clinical workflow

The clinical data and laboratory values of the patients were obtained through the hospital information operating system. A severe clinical course was defined as ICU admission and/or death in the hospital.

The criteria provided by the Chinese Center for Disease Control (CDC) were used to determine the clinical disease severity in all cases [24]. According to these criteria, mild illness was considered as asymptomatic or subtle signs of pneumonia. Patients with severe illness (dyspnea, respiratory frequency ≥30/min, blood oxygen saturation ≤93%, partial pressure of arterial oxygen to fraction of inspired oxygen ratio *<*300, and/or lung infiltrates *>*50% within 24–48 h) or critical illness (respiratory failure, septic shock, and/or multi-organ dysfunction or failure) were admitted to the ICU.

Chronic diseases in the patients' history and thrombotic complications that developed during the disease were recorded. The Fleischner classification system was used to evaluate patients with significant emphysema [25]. Patients with severe emphysema; confluent centrilobular emphysema (coalescent centrilobular/lobular radiolucencies, including multiple regions of radiolucencies that span several secondary pulmonary lobules), advanced destructive emphysema (panlobular radiolucencies, with hyperexpansion and distortion of the secondary pulmonary lobules), and substantial paraseptal emphysema (*>*1 cm diameter juxtapleural cyst-like radiolucencies or bullae, involving more than the lung apices, aligned in a row along a pleural margin) were defined. Patients with panlobular emphysema associated with alpha-1 antitrypsin deficiency were not included. A fluid depth of \geq 2 cm on chest CT was defined as prominent pleural effusion.

Between March 1 and April 15, 2020, CT examinations were routinely performed in our hospital for COVID-19 patients. Therefore, we performed CT examinations in both symptomatic and asymptomatic patients with positive RT-PCR test results in the first one and a half months. After this date, CT examination was performed only in COVID-19 patients with moderate or severe symptoms. In addition, patients with mild disease but at high risk of disease progression (depending on clinical judgment regarding the combination of age *>*65 years and presence of comorbidities, such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and immune-compromised status) underwent CT scans in line with the WHO and Fleischner Society recommendations [26,27]. Patients with suboptimal quality on CT examination (motion artifact and insufficient depth inspiration) were excluded.

Images of 901 patients were transferred to a workstation and evaluated in a single session by two radiologists, one of whom was a senior thoracic radiologist with *>*20 years of experience. The other general radiologist had *>*5 years of experience in radiology. The semiquantitative CT scores of the patients were calculated without knowing their mCHA₂DS₂-VASc scores. On CT, other findings accompanying COVID pneumonia that may have caused earlier hemodynamic deterioration of the patient (such as prominent pleural effusion, significant emphysema, pneumothorax, and pneumomediastinum) were recorded.

2.3. Semi-quantitative CT analysis (Radiological score)

Semi-quantitative CT scores were calculated based on the 5/25 model. In this model, each lobe was evaluated on a 5-point scale according to the extent of lobar involvement. (0:0%; 1: *<*5%; 2: 5–25%; 3: 26–50%; 4: 51–75%; 5: *>*75%; range 0–5; total score 0–25). Thus, the semi-quantitative CT score (radiological score) for each patient was calculated visually. (Fig. 2)

2.4. Modified CHA2DS2-VASc score analysis (Clinical score)

The modified CHA₂DS₂-VASc (mCHA₂DS₂-VASc) score for each patient was calculated retrospectively (Fig. 3).

Congestive heart failure (CHF) was defined as low ejection fraction and/or left ventricular dysfunction on echocardiography. Hypertension was defined as a blood pressure consistently above 140/90 mmHg with/ without antihypertensive drug treatment. Patients aged 65 years and older were given 1 point, and patients aged 75 years and older were given 2 points. The presence of diabetes mellitus (DM) was recorded. In addition, patients with no known history of DM but high blood glucose and/or HbA1C levels were newly diagnosed with DM. History of stroke, transient ischemic attack, or thromboembolism were recorded. Coronary artery disease (CAD) was defined as a history of myocardial infarction, percutaneous coronary intervention or coronary artery bypass grafting, or medical treatment for CAD. History of peripheral artery disease or aortic plaque was also recorded. Unlike the conventional CHA₂DS₂-VASc score, which assigns 1 point to the female sex, we assigned 1 point to the male sex in our study to calculate the mCHA₂DS₂-VASc score. Thus, each patient's mCHA₂DS₂-VASc score (clinical score) was calculated over 9 points.

2.5. R-mCHA2DS2-VASc score analysis (Radiological and clinical score)

According to the total semi-quantitative CT scores, patients with a score between 0 and 6 received 0 points, patients with 7–12 received 1 point, patients with 13–18 received 2 points, and patients with 19–25 received 3 points. We named this score the radiology-weighted score. This score was combined with the existing mCHA₂DS₂-VASc score, and the *R-mCHA₂DS₂-VASc* score (radiological and clinical score) was obtained for each patient. (Fig. 3)

2.6. CT protocol

Imaging was performed using 16-slice multidetector CT (LightSpeed VCT GE, General Electric Medical Systems WI, USA) and 192-slice dualsource multi-detector CT (Somatom Force, Siemens Healthineers, Germany). The scanning parameters were identical to the manufacturer's standard recommended pre-setting for the thorax. The area from the lung apex to the level of the diaphragm, including the costophrenic sinuses, was included in the study, and examinations were performed using low-dose techniques. Iterative reconstruction algorithms (Adaptive Statistical Iterative Reconstruction/ASIR and Advanced Modeled Iterative Reconstruction/ADMIRE) were used for the lung parenchyma, and the reconstructed images with a slice thickness of 0.625–1.25 mm were evaluated. In patients with clinical suspicion of pulmonary thromboembolism, intravenous iodinated contrast agents were administered, and pulmonary CT angiography was performed using the lowkVp technique. The obtained CT data were transferred to the workstation, and the images were evaluated on diagnostic medical monitors with 30 in., 6-megapixel resolution. In addition, coronal and sagittal multiplanar image reformations were obtained for all patients.

2.7. Statistical analysis

In this study, the data obtained from the participants were analyzed using SPSS (version IBM SPSS 22). Descriptive analysis was used to

25-50% of the left upper lobe (3 points)

50-75% of the left lower lobe (4 points)

<5% of the right upper lobe (1 point)

5-25% of the right middle lobe (2 points)

25-50% of the right lower lobe (3 points)

Fig. 2. An example of how to calculate semi-quantitative CT score in COVID-19 pneumonia on axial, sagittal, and coronal images: The total semi-quantitative CT score is $13(3 + 4 + 1 + 2 + 3)$.

	R -mCHA ₂ DS ₂ -VASc score					
	$=$ mCHA ₂ DS ₂ -VASc score (Clinical score) + Radiology weighted score calculated					
	from total semi-quantitative CT score (Radiological score)					
Total score	$(0-12) = (0-9) + (0-3)$					

Fig. 3. Components of the modified CHA₂DS₂-VASc (mCHA₂DS₂-VASc) score and *R-mCHA₂DS₂-VASc* score calculation algorithm.

evaluate the sociodemographic data. The relationship between *RmCHA2DS2-VASc,* mCHA2DS2-VASc, and CT scores was examined using the Pearson correlation test and independent *t*-test. The relationship between all three scores and the prediction of mortality and ICU admission was determined using ROC curve analysis. The chi-squared test was used when making comparisons between deceased and survivor groups. Statistical significance was set at p *<* 0.05.

3. Results

Among the patients involved in the study, 473 (52.5%) were men, and 428 (47.5%) were women. The mean patient age was 56.91 years. A total of 130 patients (14.4%) were over 75 years old, and 198 patients (22%) were between 65 and 75 years old. When we investigated the comorbidities of the patients, 357 patients had hypertension (39.6%), 260 patients had diabetes (28.9%), 113 patients had vascular atherosclerotic disease (12.5%), 93 patients had chronic kidney disease (10.3%), and 27 patients had congestive heart failure (3%). (Table 1)

In clinical follow-ups, 112 patients (12.43%) died, and 789 patients (87.56%) survived. In total, 189 (21%) of the 901 patients required intensive care. In the ICU, 32 patients (3.6%) required high-flow nasal oxygen (HFNO), 32 patients (3.6%) required non-invasive mechanical ventilation (NIMV), and 119 patients (13.2%) required invasive mechanical ventilation (IMV). The remaining six ICU patients did not require any further ventilator therapy other than nasal oxygen therapy.

There was a significant age difference between the deceased and

surviving groups, whereas there was no significant difference in terms of sex distribution. Accordingly, mortality was mostly observed in patients aged 75 years and over (50.9%). Similarly, patients in the deceased group were significantly older than those in the surviving group. (54.71 ± 15.66 vs. 72.39 ± 11.43, p *<* 0.001)

Comorbidities, including HT, DM, cardiovascular atherosclerotic disease, and CKD, in the deceased group were significantly higher than that in the surviving group (p *<* 0.001), whereas there was no significant difference between the groups in terms of CHF.

Thrombotic complications occurred in 39 patients (4.3%) during the clinical follow-ups, and the patient distribution was as follows: deep vein thrombosis (DVT) in four patients (0.4%), pulmonary thromboembolism (PTE) in 10 patients (1.1%), non-ST-elevated myocardial infarction (NSTEMI) in 15 patients (1.7%), ST-elevated myocardial infarction (STEMI) in three patients (0.3%) and stroke in seven patients (0.8%). Some accompanying findings were recorded that could disrupt the patient's hemodynamics. These included pneumothorax ($n = 7$, 0.8%), isolated pneumomediastinum without pneumothorax ($n = 2$, 0.2%), pleural effusion measuring \geq 2 cm (n = 32, 3.6%), and significant emphysema ($n = 22, 2.4\%$). Six of the seven pneumothorax cases were observed in the deceased group. Chi-square analysis was invalid in all complication groups owing to insufficient cell distribution.

The patient groups were compared in terms of semi-quantitative CT, mCHA2DS2-VASc, and *R-mCHA2DS2-VASc* scores (Table 2).

The semi-quantitative CT scores (14.75 \pm 5.49), mCHA₂DS₂-VASc score (4.09 \pm 1.54), and *R-mCHA₂DS₂-VASc* score (6 \pm 1.59) were

Table 1

significantly higher in the deceased group than that in the surviving group (p *<* 0.001). In addition, a moderately positive significant correlation was found between mCHA₂DS₂-VASc and CT scores ($r = 0.407$, p *<* 0.05).

ROC curve analysis was performed to determine the requirement of intensive care and mortality of semi-quantitative CT score, mCHA₂DS₂-VASc score, and *R-mCHA2DS2-VASc* score (Graphics 1 and 2, Tables 3 and 4).

When the threshold value for the semi-quantitative CT score predicting ICU admission was 14, the sensitivity was 83.6%, and the specificity was 79.2%; when the threshold value for the mCHA₂DS₂-VASc score was 5, the sensitivity was 78.8%, and the specificity was 81%; and when the threshold value for *R-mCHA₂DS₂-VASc* score was 6, the sensitivity was 89.4%, and the specificity was 87.5%.

When the threshold value that can predict mortality was 19 for the

semi-quantitative CT score, the sensitivity was 83.9%, and the specificity was 81.5%; when the threshold value for the mCHA₂DS₂-VASc score was 6, the sensitivity was 82.1%, and the specificity was 75.7%; when the threshold value for the *R-mCHA₂DS₂-VASc* score was 8, the sensitivity was 83.9%, and the specificity was 91.6%.

The *R-mCHA2DS2-VASc* score was superior to the semi-quantitative CT and mCHA2DS2-VASc scores in predicting mortality and ICU admission (Graphics 1 and 2).

4. Discussion

Most symptomatic patients (80%) with COVID-19 experience mildto-moderate respiratory illness and recover without the requirement of special treatment. In patients with severe symptoms, dyspnea and hypoxia are more pronounced [24]. The lung involvement rate tends to be *>*50% in the imaging obtained two days after the symptom onset in serious and critically ill patients [28]. Old age is associated with a higher mortality rate, and it has been reported that 80% of COVID-associated deaths occur in the age group of 65 years old and over [16,29]. In addition, sociodemographic studies show that men are more frequently affected by *SARS CoV-2* infection, and the in-hospital mortality rate was higher in males than in females [17,18]. In our study, in accordance with the literature, a significant difference was found between the groups in terms of age distribution, but no significant difference was observed in terms of gender distribution, which may be caused by the small sample

Table 3 and Graphic 1

ROC curve and analysis table of semi-quantitative CT, mCHA₂DS₂-VASc, and *RmCHA2DS2-VASc* scores in predicting the need for ICU admission.

Table 2

Comparison of patient groups in terms of CT, mCHA2DS2-VASc, and *R-mCHA2DS2-VASc* score.

Table 4 and Graphic 2

ROC curve and analysis table of semi-quantitative CT, mCHA₂DS₂-VASc, and *RmCHA2DS2-VASc* scores in mortality prediction.

	AUC (%95 CD	C ₁₁₁ off value	P value	Sensitivity (%)	Specificity (%)
$mCHA2DS2$ - VASc score	0.88 $(0.84 - 0.91)$	>6	< 0.001	82.1	75.7
CT score	0.89 $(0.86 - 0.93)$	>19	< 0.001	83.9	81.5
R -mCHA ₂ DS ₂ - VASc score	0.95 $(0.93 - 0.97)$	> 8	< 0.001	83.9	91.6

size. Moreover, mortality was mostly observed in individuals aged 75 years and older (50.9%). An increased risk of serious clinical course and death due to COVID-19 has been reported in patients with cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer, obesity, and chronic kidney disease [24,30,31]. Zheng et al. revealed that patients with comorbidities such as hypertension, diabetes, and cardiovascular disease have a greater risk of developing a critical illness [32]. In a meta-analysis, Krittanawong et al. reported that patients with clinically severe and critical COVID-19 disease had a statistically significantly higher rate of DM, HT, CAD, and CHF in their history compared to non-serious COVID-19 disease [33]. In a retrospective study of approximately 250,000 patients nationwide in Brazil, increased mortality was reported in patients with three or more comorbidities $[18]$. In our study, in line with the literature, HT (n = 97, 86.6%), DM ($n = 65$, 58%), cardiovascular atherosclerotic disease ($n =$ 48, 42.9%), and CKD ($n = 47$, 42%) were significantly higher in the deceased group (p *<* 0.001). However, a significant relationship between CHF and mortality has not yet been established. This may be due to incomplete reporting and/or underdiagnosis.

Clinical studies have shown that both susceptibility to COVID-19 and poor outcomes are associated with cardiovascular diseases [34]. All components of the CHA2DS2-VASc score are important cardiovascular risk factors. In clinical practice, the $CHA₂DS₂-VASC$ score is primarily used to predict the risk of stroke in patients with atrial fibrillation. However, in other conditions, such as CHF, it is a well-validated risk stratification score used to predict morbidity and mortality [15]. In a retrospective and multicenter study of 349 COVID-19 patients, it was reported that the CHA₂DS₂-VASc score significantly predicted inhospital mortality in COVID-19 patients [14]. Furthermore, another study with a sample of 694 RT-PCR positive patients has shown that the mCHA2DS2-VASc score was superior to the CHA2DS2-VASc score in predicting in-hospital mortality [35]. In the same study, it was reported that the mCHA₂DS₂-VASc score is an independent predictive factor for mortality. The in-hospital mortality rate increased significantly in patients whose mCHA₂DS₂-VASc score was \geq 4 points. Similar to the

literature, significant statistical results were obtained in this study for predicting ICU admission and mortality using the $mCHA₂DS₂-VASC$ score.

In the computer-aided volume-based quantitative scoring method used by Colombi et al., they found an increase in rate of ICU admission in cases whose the lung parenchyma area with good ventilation was *<*73% [6]. In a study that examined 262 cases with COVID-19 pneumonia, it was reported that when the threshold value in the semi-quantitative CT score was selected as 12, the sensitivity was 69.6%, and the specificity was 80.1% [36]. Another study, with a sample of 130 symptomatic COVID-19 patients, investigated the relationship between semiquantitative CT score and short-term (24-day) mortality, it was found that a score of 18 and above was significantly associated with an increased risk of death [37]. In line with the literature, our study demonstrated significant statistical results in predicting ICU admission and mortality.

In a single-center study of 301 patients, the accuracy of the CT score in predicting unfavorable outcomes increased when combined with some demographic characteristics (age and sex), comorbidities (hypertension and ischemic heart disease), and laboratory data (WBC and AST) [19]. Similarly, the *R-mCHA₂DS₂-VASc* score (radiological and clinical score) was superior to other scores in predicting mortality and ICU admission.

The limitations of this study include its retrospective design. Although CKD patients were found to be significantly higher in the deceased group in this study, this was not among the components of the *R-mCHA2DS2-VASc* score. This situation has been considered a potential reason for the decrease in the sensitivity and specificity of the *RmCHA2DS2-VASc* score. We developed and tested a new model, *RmCHA2DS2-VASc* score, based on the patient population from the first wave. Thus, our study lacked an analysis of *SARS-CoV 2* genome variants. Given that new variants have emerged since the onset of the COVID-19 pandemic, this model needs to be tested in a population with new dominant COVID variants. Nevertheless, it has been shown in this study that the *R-mCHA2DS2-VASc* score gives better results compared to other scoring methods. Further prospective studies with larger sample groups are needed for widespread clinical use.

In conclusion, early prediction of ICU admission and mortality risk in COVID-19 patients is of great importance for clinical patient management and treatment strategies. The *R-mCHA₂DS₂-VASc* score defined in this study has sufficient sensitivity and specificity and has been successful in predicting a severe clinical course in the early period. Unlike other scores, it includes both clinical and radiological parameters, making it a strong prognostic indicator.

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IRB statement

This retrospective study was approved by the institutional review board, and the requirement of written informed consent was waived.

Contributors

Mehmet Can Pençe designed the study, evaluated CT examinations, undertook the formal analysis, calculated radiological scores, and wrote the original draft. Aydan Avdan Aslan contributed to writing, reviewing, and editing. Özlem Güzel Tunçcan took part in clinical follow-up and evaluated clinical score. Gonca Erbas¸ contributed to the conceptualization of the study, formal analysis, writing, editing, evaluated CT examinations, project administration, and supervised the study. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

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

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