Atrial Fibrillation and Cardiovascular Risk Assessment among COVID-19 Patients Using Different Scores

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Abstract: Since the advent of severe acute respiratory syndrome-coronavirus-2 in December 2019, millions of people have been infected and succumbed to death because of this deadly virus. Cardiovascular complications such as thromboembolism and arrhythmia are predominant causes of morbidity and mortality. Different scores previously used for atrial fibrillation (AF) identification or prediction of its complications were investigated by physicians to understand whether those scores can predict in-hospital mortality or AF among patients infected with the severe acute respiratory syndromecoronavirus-2 virus. Using such scores gives hope for early prediction of atrial arrhythmia and in-hospital mortality among coronavirus disease 2019–infected patients. We have discussed the mechanisms of AF and cardiovascular damage in coronavirus disease 2019 patients, different methods of AF prediction, and compared different scores for prediction of in-hospital mortality after this viral infection.

Key Words: atrial fibrillation, CHA2DS2VASc score, COVID-19, in-hospital mortality, thromboembolism

As of January 2022, more than 292 million people around the world have been infected with coronavirus disease 2019 (COVID-19), with 5 million lives lost.[1] Because of the highly contagious infection and high rate of hospitalization (nearly 10% in older patients) and mortality, this viral infection became a concern after the infection emerged in Wuhan, China in late 2019.[2] Arrhythmia, myocarditis, heart failure, pulmonary embolism, and disseminated intravascular coagulation are the most common cardiovascular complications of COVID-19.[3] After the respiratory complications, new-onset atrial fibrillation (AF) is the second most common complication of COVID-19 infection.[4]

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The scoring systems using congestive heart failure, hypertension, age, diabetes mellitus, stroke, sex and vascular disease (more commonly known as CHADS(2) and CHA(2)DS(2)-VASc) are well established for the prediction of stroke among AF patients.[5] The choice of anticoagulation also depends on these two risk-scoring systems. Along with other scores, these scores were tested to predict AF among COVID-19 and non-COVID-19 patients; similarly, they were tested for the prediction of hospitalization as well as cardiovascular mortality. We discuss the different cardiovascular scores that were investigated in different studies with a focus on scores for prediction of AF among COVID-19 patients.

AF in COVID-19 Patients

The most common cardiovascular complications in COVID-19 patients are arrhythmia (AF or ventricular tachyarrhythmia), elevation of cardiac biomarkers, myocarditis, pulmonary embolism, and other thromboembolic manifestations.[3] AF is the most prevalent arrhythmia in COVID-19 infection, and is detected in 19% to 21% of all cases.[6,7]

Severe acute respiratory syndrome-coronavirus-2, the virus responsible for COVID-19 infection, binds to transmembrane angiotensin-converting enzyme 2 on type 2 pneumocytes, perivascular pericytes, and cardiomyocytes, leading to cellular damage or

Key Points

- Cardiac arrhythmia, namely atrial fibrillation (AF) and thromboembolism, are frequently observed complications in hospitalized coronavirus disease 2019 (COVID-19) patients.
- The pathophysiology of cardiovascular damage and the development of AF caused by COVID-19 are explained by various studies.
- Different clinical scores are developed to predict thromboembolism among patients with AF. Different modified scores also are tested to predict AF and cardiovascular complications other than thromboembolism.
- Using previously known cardiovascular scoring systems to identify AF and COVID-19-related mortality are still being studied. A handful of studies have investigated the usefulness of scoring to predict AF and in-hospital mortality among COVID-19 patients.

dysfunction, which may lead to lung injury, vascular damage, and myocarditis, respectively. It also may cause endothelial dysfunction, microvascular dysfunction, and plaque instability, leading to myocardial infarction.[3]

Dysfunctional microvascular or endothelial cells lead to myocardial inflammation, fibrosis, tissue edema, and interstitial hydrostatic pressure, which may be the cause of AF development. Pulmonary hypertension, T cells, and angiotensin also may play some role[8] in the development of AF.

New-onset AF (NOAF) in COVID-19 patients is related to significantly worse outcomes. After adjusting for confounding variables, individuals with NOAF showed 14 times higher odds of having (odds ratio [OR] 14.26) thromboembolism (95% confidence interval [CI] 2.86–71.10, $P < 0.001$).[9] AF is more common among older, hypertensive patients[9,10] and those with more comorbidities.[10] A meta-analysis showed that approximately 8% of hospitalized COVID-19 patients had AF (95% CI 6.3–10.2) and they have a 3.97-fold increased chance of all-cause mortality (95% CI 2.76–5.71).[10]

Similarly, preexisting AF also is associated with increased short-term mortality, as shown by Zuin et al.[11] In their systematic review and meta-analysis they showed that there is a higher risk of short-term death (OR 2.22, 95% CI 1.47–3.36) among patients who had AF before they contracted the COVID-19 infection.[11]

Predicting COVID-19–Related Morbidity and Mortality

In UK Biobank participants, age group, sex, ethnicity, education, preexisting dementia, diabetes mellitus, chronic obstructive airway disease, pneumonia, depression, AF, and hypertension emerged as independent risk factors for hospitalization in COVID-19–infected patients, wheras the first five factors were statistically significant for mortality. Moreover, chronic kidney disease and asthma were risk factors for COVID-19 hospitalization among females.[12] In a retrospective cohort study originating in New York City, Chilimuri et al showed that old age, a D-dimer >1000 ng/mL during admission, >200 mg/dL of C-reactive protein (CRP) and low leukocyte count were associated with higher mortality among hospitalized COVID-19 patients.[13]

A simple electrocardiogram (ECG) may be helpful for the risk stratification of COVID patients. According to Lanza et al, most ECG variables were significantly associated with mortality, in which QRS duration >110 ms, left bundle branch block, and presence of any ECG abnormality were independently associated with increased mortality.[14]

The Braden Scale, commonly used for identifying pressure ulcer risk among hospitalized patients, was investigated by Lovicu et al for sorting out high-risk patients from those who are admitted in general wards.[15] Patients with COVID who have a Braden Scale score of ≤15 had significantly higher rates of in-hospital mortality.[15]

Another study evaluated the predictability of the CHA(2)DS(2)-VASc Score for in-hospital mortality among COVID-19 patients, regardless of AF. The score was higher in nonsurvivor COVID-19 patients ($P < 0.001$), and logistic regression analysis demonstrated admission CHA(2)DS(2)-VASc ≥3 (OR 12.612, 95% CI 3.092–51.451), leukocyte count (OR 1.327, 95% CI 1.145–1.538), CRP (OR 1.010, 95% CI 1.002–1.018), and ferritin level (OR 1.005, 95% CI 1.003–1.007) were independently associated with mortality among COVID-19 patients.[16]

Subsequently, Abacioglu and Yildirim compared the predictive value of anticoagulation and risk factors in AF (ATRIA) and modified-CHA(2)DS(2)-VASc (m-CHA(2)DS(2)-VASc) scores for in-hospital mortality in COVID-19. In a multivariate logistic regression analysis, both scores were independently predicting in-hospital mortality. The receiver operating characteristic curve showed that ATRIA was superior to the m-CHA2DS2-VASc score, with an area under the curve (AUC) of 0.774.[17]

The Modified ATRIA Risk Score (M-ATRIA-RS) was used to predict in-hospital mortality in COVID-19 patients and to compare with modified CHA(2)DS(2)-VASc (m-CHA(2)DS(2)-VASc)-RS, ATRIA, and the Charlson Comorbidity Index to identify its discrimination capability. Multivariate logistic regression analysis showed that M-ATRIA-RS, malignancy, increased troponin, and lactate dehydrogenase were independent predictors of in-hospital mortality ($P < 0.001$). An increased M-ATRIA-RS score was associated with adverse clinical outcomes. In a receiver operative characteristics analysis, the discriminative ability of M-ATRIA-RS was superior to mCHA(2)DS(2)-VASc-RS and ATRIA-RS. Although it was similar to the Charlson Comorbidity Index score, it is easier to calculate.[18]

A retrospective multicenter cohort study was performed in the United States to predict the chance of hospitalization and in-hospital mortality using electronic health records. Three scores, namely green, yellow, and red scores were developed to see the predictability. Yellow and red scores were compared with green scores and it was found that they have higher odds of hospitalization as well as in-hospital mortality.[19]

In 2021, Uribarri et al analyzed the international Hopkins Opportunities for Participant Engagement Registry and found the CHA(2)DS(2)-VASc score acceptably predicts 60-day mortality in COVID-19 patients (AUC 0.748, 95% CI 0.733–0.764), but not its embolic risk (AUC 0.411, 95% CI 0.147–0.675).[20]

Similarly, another study found that the CHADS(2), CHA(2)DS(2)-VASc, and CHA(2)DS(2)-VASc-M scores are significantly associated with all-cause mortality but not with thromboembolic events in COVID-19 patients. Mortality was significantly higher with increasing scores for the three scores mentioned; of these, the CHA(2)DS(2)-VASc-M showed the best predictive value for mortality (AUC 0.820).[21]

Parameters to Identify Stroke and Other Morbidities Caused by AF

In the Framingham Heart Study, a prospective, community-based study using an observational cohort in Framingham, Massachusetts, a risk score for stroke or death was developed. To sort out patients

who have AF, a CHADS(2) score was derived that included the following risk predictors of future stroke: congestive heart failure, systolic blood pressure, advancing age, female sex, diabetes mellitus, prior stroke, or transient ischemic attack.[22]

But for patient with AF and CHADS(2) score of 0 to 1, it became difficult to make a decision about anticoagulation, then CHA(2)DS(2)-VASc derived by Olsen et al.23 which provides critical information on risk of stroke in AF patients that can guide the use of anticoagulation in such patients. The CHA(2)DS(2)-VASc score can help us identify patients with an increased risk of stroke among those with AF and a low CHADS(2) score. A CHA(2)DS(2)-VASc score of zero can more accurately identify subjects who are truly low risk.[23]

In addition to predicting stroke risk, CHADS(2) and CHA(2)DS(2)-VASc scores were investigated to determine their predictability of the first cardiovascular hospitalization in patients with AF or atrial flutter, thereby identifying at-risk patients and guiding therapy. These scores were the top two predictors of hospitalization after diagnosis of AF or atrial flutter. The risk of hospitalization was increased 2.3 to 2.7 times in patients with CHADS(2) scores of 6 and increased to nearly 3 times in patients with CHA(2)DS(2)-VASc scores of 9 compared with patients with a score of zero.[24]

AF among patients admitted to the intensive care unit was studied by Moss et al.[25] They found that 19% of their intensive care unit patients had some form of AF; interestingly, 8% of them had NOAF, which was subclinical or undocumented. The strongest predictors of NOAF in these patients were old age, acute respiratory failure, and sepsis. Clinical NOAF was associated with high in-hospital mortality (OR 1.63, 95% CI 1.01–2.63) and longer hospital stay (OR 2.25, 95% CI 0.58–3.92), but it was not associated with survival after hospital discharge (hazard ratio 0.99, 95% CI 0.76–1.28).[25]

Predictors of AF Development

With the increasing longevity of individuals across the world, particularly in the United States, the prevalence and incidence of AF also will increase. According to a study in 2010, the incidence of AF was nearly 1.2 million cases, which will increase to approximately 2.6 million in 2030, and the prevalence of AF in 2030 will be 12.1 million cases, approximately 3 times the prevalence in 2010.[26] As such, predicting AF is a necessity to better managing the increasing burden of this condition.

Because inflammation is an essential step in AF development, neopterin, a biomarker of cellular immune activation, was investigated, and it was found that a higher plasma level of this biomarker is associated with an increased risk of incident AF after adjustment of age, sex, body mass index, current smoking, diabetes mellitus, high blood pressure, and renal function in hospitalized patients. When both neopterin and CRP levels are elevated in the blood, the highest association with AF was revealed in two separate cohorts (hazard ratio 1.54 and 1.67), which was statistically significant.[27]

A simple score was developed to predict AF among septic patients, and it was determined that this score yielded good discrimination (C statistic 0.81, 95% CI 0.79–0.84) and significance (χ^2test 9.39, $P = 0.31$) for daily prediction of AF occurrence.[28] It is noteworthy that AF is a common complication of sepsis and independently associated with higher mortality.[29,30]

The CHA(2)DS(2)-VASc score can predict NOAF in hospitalized community-acquired pneumonia. A study by Pieralli et al among 468 patients (median age 76 years) showed CHA(2)DS(2)-VASc >3 was the most accurate cutoff for a prediction of NOAF (AUC 0.653).[4]

Meanwhile, the C_2HEST score was found to be superior to the CHADS(2) and CHA(2)DS(2)VASc scores among a Chinese population to predict the development of AF.[31] Li et al used coronary artery disease/chronic obstructive pulmonary disease, hypertension, age older than 75 years, systolic heart failure, and hyperthyroidism as predictors of AF. Later, both CHA(2)DS(2)-VASc and C_2HEST scores were assessed to determine the predictability of AF development among end-stage renal disease, but both scores yielded almost identical AUCs (0.578 and 0.598, respectively), which signifies that they have almost no predictability for AF among patients with end-stage renal disease.[32]

CHADS(2) and CHA(2)DS(2)VASc were originally developed to predict thromboembolic stroke among patients with AF, but there are studies that have tried to use these scores along with the HATCH ($1 \times$ [hypertension] + $1 \times$ [age > 75 years] + $2 \times$ [transient ischemic attack or stroke] + $1 \times$ [chronic obstructive pulmonary disease] + $2 \times$ [heart failure]) score[33] to predict AF among patients who had already had a stroke. The CHADS(2) score had the lowest C-statistic (0.558–0.597), whereas the CHA(2)DS(2)VASc score had comparable C-statistics (0.603–0.644) to the HATCH score (0.612–0.653) in predicting an AF diagnosis after stroke.[34]

Of note, the HATCH score was developed by de Vos et al,[33] taking into account heart failure, age, previous transient ischemic attack or stroke, chronic obstructive pulmonary disease, and hypertension to predict the development of persistent AF after the initial diagnosis of AF among hospitalized patients. They found that 50% of patients who have a HATCH score > 5 will have sustained AF, whereas only 6% will have sustained AF if the score is zero.[33]

Predicting AF in COVID-19 Patients

In general, AF is associated with higher comorbidities such as stroke and major bleeding, as well as all-cause mortality.[35] Because AF is the most prevalent arrhythmia among COVID-19 patients[6,7] and NOAF is associated with a 14 times higher chance of having thromboembolic manifestations[9] and increased comorbidities,[36] early detection of AF in COVID-19 patients is warranted.

In a single-center study including the data of 658 COVID-19 patients who were hospitalized, Kelesoglu et al revealed that the

CHA(2)DS(2)-VASc score was higher in patients who developed NOAF compared with those who did not.[29] Age, CHA(2)DS(2)-VASc score, CRP, erythrocyte sedimentation rate, and presence of diffuse lung infiltration on chest computed tomography (CT) may be used to identify patients at high risk for the development of NOAF. Especially among these parameters, the presence of diffuse lung infiltration on chest CT was the most powerful independent predictor of NOAF development.[29] In this study, they also found that a higher CHA(2)DS(2)VASc score (3.42 ± 0.56) is significantly associated with NOAF among hospitalized COVID-19 patients (adjusted OR 2.51; 95% CI 1.18–5.33). Diffuse infiltrates on chest CT had the highest OR (24.44; 95% CI 3.90–152.99).[29]

Conclusions

Due to the unguarded spread of severe acute respiratory syndrome-coronavirus-2 across the globe-despite the development of multiple vaccines, COVID-19–related vascular complications remain a major health concern. Identifying COVID-associated AF with different scores as well as predicting other comorbidities such as thromboembolism is vital for healthcare service. Understanding the mechanism of COVID-19–related cardiovascular complications is a significant step to treat this condition. Using different scores to predict AF and in-hospital mortality among COVID patients will help healthcare workers in making decisions earlier to prevent inadvertent complications.

Scores such as C_2HEST and CHA(2)DS(2)VASc-M may need to be validated to determine whether they have better prediction for AF among COVID-19 patients in comparison to CHA(2)DS(2)VASc. Larger studies can incorporate these scores to validate the predictability of AF that is associated with higher mortality.

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