Utilizing Coronary Artery Calcification and the COVID-GRAM Score to Predict Critical Illness in COVID-19 Patients

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ABSTRACT

Introduction: Coronary artery calcification (CAC), identified on routine chest computed tomography (CT), has been associated with worse outcomes in hospitalized patients with COVID-19. The COVID-GRAM Score is a risk stratification tool developed to predict critical illness in this population. This study compared the predictive performance of CAC identified on chest CT with that of the COVID-GRAM Score for intensive care unit (ICU) admission among hospitalized patients with COVID-19 and evaluated whether combining these measures improved identification of high-risk patients. We hypothesized that CAC would outperform the COVID-GRAM Score.

Methods: This retrospective cohort study includes 238 adults hospitalized with COVID-19 at a large academic medical center in Milwaukee, Wisconsin, between July 1, 2020, and July 1, 2021. Data were obtained through electronic medical record database queries and chart review. Eligible patients had confirmed COVID-19 infection and no prior history of coronary artery disease.

Results: Statistical analyses included descriptive statistics, sensitivity and specificity analyses, and receiver operating characteristic (ROC) curve analysis. The mean age was 64 [SD, 15] years, and 46.2% of patients were women. Patients admitted to the ICU had higher mean COVID-GRAM Scores than those not admitted to the ICU (mean [SD], 168 [45.4] vs 150 [44]; $P = .01$). Any CAC was present in 54.2% of ICU-admitted patients compared with 39.1% of patients not admitted to the ICU, and severe CAC was more common among ICU-admitted patients (18.6% vs 5.6%). The area under the ROC curve (AUC) was 0.61 for illness risk score derived from the COVID-GRAM model, compared with 0.58 for any CAC and 0.57 for severe CAC. Composite measures combining CAC and illness risk score did not improve discriminatory performance.

Conclusions: Neither the COVID-GRAM Score nor CAC effectively predicted ICU admission among hospitalized patients with COVID-19. Combining CAC with the illness risk score did not significantly improve predictive performance, highlighting the need for more robust risk stratification tools.

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INTRODUCTION

COVID-19 has caused more than 700 million cases and over 7 million deaths globally and was the 10th leading cause of death in the United States in 2023 (approximately 75 000 deaths).[1-3] Growing evidence points to its impact on cardiovascular health, increasing the risk of myocarditis, arrhythmias, and thromboembolic events in addition to known respiratory complications.[4,5] Using scoring systems to identify patients at risk for deterioration early could lead to better patient outcomes and more efficient use of health care resources.[6]

Coronary artery calcification (CAC) is detectable on computed tomography (CT) and reflects the burden of atherosclerotic disease. Elevated CAC levels signify heightened cardiovascular risk and are associated with greater susceptibility to adverse events. CT scans and the Agatston scoring system quantify CAC, aiding risk assessment and prompting interventions such as lifestyle changes and pharmacotherapy.[7-9] CAC identified on routine chest CT independently predicts worse outcomes among hospitalized patients with COVID-19, including higher mortality, more severe acute coronary syndromes, and increased need for mechanical ventilation.[1,10] This association persists even after accounting for established risk factors, suggesting the unique value of CAC in refining prognosis.

The COVID-GRAM Score is a risk tool developed to stratify hospitalized patients with COVID-19 according to their likelihood of adverse outcomes, with higher scores associated with a worse prognosis. The score's effectiveness at hospital admission may facilitate early risk stratification and potentially inform treat-

ment decisions.[11] A retrospective cohort study involving patients from 575 hospitals in China used data collected through January 31, 2020, to develop the score; however, it requires further evaluation in diverse external populations to establish validity.

While both CAC and the COVID-GRAM Score are potentially valuable tools for predicting outcomes in patients with COVID-19, studies evaluating their utility are scarce and have limitations. Building on our prior work demonstrating an association between CAC and worse COVID-19 outcomes,[1] this study compares the predictive ability of CAC detected on chest CT scans with that of the COVID-GRAM Score. We hypothesized that CAC would outperform the COVID-GRAM Score in predicting critical illness, defined by intensive care unit (ICU) admission. As a secondary objective, we assessed whether combining CAC and the COVID-GRAM Score would improve discrimination of ICU-level care.

METHODS

The Medical College of Wisconsin Institutional Review Board approved this retrospective cohort study and waived individual informed consent on May 21, 2020.

Data Source and Study Population

To identify eligible patients, researchers used the Clinical Research Data Warehouse tools, including i2b2 and the Honest Broker tool, provided by our institution's Clinical and Translational Science Institute. Researchers conducted a chart review using the institution's electronic health record to collect data.

Patients aged 18 years or older without a history of coronary artery disease (prior myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting) who were hospitalized at a large academic medical center in Milwaukee, Wisconsin, with active COVID-19 infection confirmed by reverse transcription-polymerase chain reaction (RT-PCR) between July 1, 2020, and July 1, 2021, were included. Patients who had previously tested positive for COVID-19 but did not have active symptoms during hospitalization and those who did not undergo chest CT during hospitalization were excluded.

The original dataset contained 464 participants. Individuals with missing lactate dehydrogenase values (n = 236) were excluded because the COVID-GRAM Score could not be calculated without this variable.[1] After application of these criteria, the final sample comprised 238 individuals.

Independent Variables and Outcome

The independent variables included demographic characteristics (age, sex, ethnicity, race, marital status, and employment status), CAC, and COVID-GRAM Score-related variables. Variables required to calculate the COVID-GRAM Score included chest radiograph abnormalities, age, hemoptysis, dyspnea, unconsciousness, number of comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary artery disease, heart failure, chronic kidney disease, cancer, cerebrovascular disease, hepatitis B, immunodeficiency), cancer history, neutrophil-to-lymphocyte ratio, lactate dehydrogenase, and direct bilirubin. The points assigned in the COVID-GRAM Score are converted to an illness risk score, defined as risk of ICU admission, invasive ventilation, or death.[11]

Table 1. Demographic Characteristics (n = 238)

Variable	ICU – No (n = 179)	ICU – Yes (n = 59)	Overall (n = 238)	*P* value
Age, mean [SD], y	62.7 [15.1]	65.6 [13.7]	63.5 [14.8]	.2
Sex, n (%)				.94
Female	83 (46.4)	27 (45.8)	110 (46.2)	
Male	96 (53.6)	32 (54.2)	128 (53.8)	
Ethnicity, n (%)				.86
Hispanic	7 (3.9)	2 (3.4)	9 (3.8)	
Non-Hispanic	172 (96.1)	57 (96.6)	229 (96.2)	
Race, n (%)				.27
Black/African American	31 (17.4)	16 (27.1)	47 (19.8)	
White	130 (73.0)	38 (64.4)	168 (70.9)	
Other	17 (9.6)	5 (8.5)	22 (9.3)	
Marital status, n (%)				.37
Married	103 (57.5)	30 (50.8)	133 (55.9)	
Not married	76 (42.5)	29 (49.2)	105 (44.1)	
Employment status, n (%)				<.01
Employed	70 (39.3)	11 (18.6)	81 (34.2)	
Not employed	108 (60.7)	48 (81.4)	156 (65.8)	

Based on the illness risk score, patients were categorized into 1 of 3 risk groups: low, intermediate, and high risk. The low-risk group included patients with an illness risk score of <1.7%. The intermediate-risk group included patients with an illness risk score of 1.7% to <40.4%, and the high-risk group included patients with an illness risk score of ≥40.4%. For this study, the high-risk group (illness risk score of ≥40.4%) was classified as positive as a binary variable (positive illness risk score).

In addition to COVID-19-related factors, the severity of CAC detected on CT was evaluated. Radiologists assigned CAC severity as none, mild, moderate, or severe. These categories were subsequently grouped into 3 classifications for analysis: any CAC, moderate-to-severe CAC, and severe CAC.

Composite scoring systems were created by combining CAC severity and positive illness risk score. The first composite score combined any CAC and positive illness risk score (Composite 1). The second combined moderate-to-severe CAC and positive illness risk score (Composite 2). The third combined severe CAC and positive illness risk score (Composite 3). The binary dependent (outcome) variable was whether participants required ICU admission.

Statistical Analysis

Descriptive analyses were conducted to summarize the demographic and clinical characteristics of the study population.

Continuous variables were summarized as means with standard deviations, and categorical variables were summarized as frequencies and percentages. Differences between patients admitted to the ICU and those not admitted were evaluated using *t* tests for continuous variables and chi-square tests for categorical variables.

To assess the discriminatory performance of clinical measures for predicting ICU admission, binary classification analyses were performed. ICU admission was treated as a binary outcome (yes/no). The illness risk score (derived from the COVID-GRAM model) was evaluated as a continuous variable and dichotomized using a threshold of 0.404 to define high-risk versus non-high-risk groups.[11] CAC was examined using 3 binary categorizations: (1) any CAC versus none, (2) moderate-to-severe CAC versus none or mild CAC, and (3) severe CAC versus all other CAC categories.

For each predictor variable, 2x2 contingency tables were generated to classify ICU admission as true positive, false positive, true negative, or false negative, from which sensitivity and specificity were calculated. Composite predictors that combined clinical risk and CAC burden also were evaluated: (1) high illness risk score with any CAC, (2) high illness risk score with moderate-to-severe CAC, and (3) high illness risk score with severe CAC. Receiver operating characteristic (ROC) analyses were performed by comparing predictor values with observed ICU admission status. ROC curves were constructed by plotting sensitivity against 1 – specificity, and the area under the ROC curve (AUC) was used to summarize discriminative accuracy.

All statistical analyses were performed using R version 4.2.3 (R Foundation for Statistical Computing), and *P* values <.05 were considered statistically significant.

Table 2. COVID-GRAM Score, Illness Risk Score, CAC Scores, and Composite Scores

Variable	ICU – No (n = 179)	ICU – Yes (n = 59)	Overall (n = 238)	*P* value
COVID-GRAM Score, mean [SD]	150 [44.0]	168 [45.4]	155 [44.9]	.01
X-ray abnormality, n (%)				.77
No	51 (28.5)	18 (30.5)	69 (29.0)	
Yes	128 (71.5)	41 (69.5)	169 (71.0)	
Hemoptysis, n (%)				.99
No	167 (93.3)	59 (100)	226 (95.0)	
Yes	12 (6.7)	0 (0)	12 (5.0)	
Dyspnea, n (%)				.2
No	48 (26.8)	21 (35.6)	69 (29.0)	
Yes	131 (73.2)	38 (64.4)	169 (71.0)	
Unconsciousness, n (%)				.81
No	174 (97.2)	57 (96.6)	231 (97.1)	
Yes	5 (2.8)	2 (3.4)	7 (2.9)	
No. of comorbidities, mean [SD]	3.08 [1.66]	3.76 [1.50]	3.25 [1.65]	<.01
Cancer history, n (%)				.53
No	129 (72.1)	45 76.3)	174 (73.1)	
Yes	50 (27.9)	14 23.7)	64 (26.9)	
Neutrophil-lymphocyte ratio, mean [SD]	8.50 [7.83]	14.4 [18.8]	9.98 [11.8]	<.01
Lactate dehydrogenase, mean [SD]	369 [164]	472 [188]	394 [175]	<.001
Direct bilirubin, mean [SD]	2.61 [2.96]	2.78 [2.84]	2.65 [2.92]	.69
Illness risk score, mean [SD][a]	51 [31.7]	62.7 [27.7]	53.9 [31.1]	.01
Any CAC (mild/moderate/severe), n (%)				.04
No	109 (60.9%	27 (45.8)	136 (57.1)	
Yes	70 (39.1)	32 (54.2)	102 (42.9)	
Moderate-to-severe CAC, n (%)				.22
None or mild	144 (80.4)	43 (72.9)	187 (78.6)	
Moderate or severe	35 (19.6)	16 (27.1)	51 (21.4)	
Severe CAC, n (%)				<.01
None or mild or moderate	169 (94.4)	48 (81.4%)	217 (91.2)	
Severe	10 (5.6)	11 (18.6%)	21 (8.8)	
Composite 1, n (%)				<.01
Positive illness risk score[b] and any CAC	54 (30.2)	30 (50.8)	84 (35.3)	
Other	125 (69.8)	29 (49.2)	154 (64.7)	
Composite 2, n (%)				.06
Positive illness risk score[b] and moderate-to-severe CAC	29 (16.2)	16 (27.1)	45 (18.9)	
Other	150 (83.8)	43 (72.9)	193 (81.1)	
Composite 3, n (%)				<.01
Positive Illness Risk Score[b] and severe CAC	9 (5.0)	11 (18.6)	20 (8.4)	
Other	170 (95.0)	48 (81.4)	218 (91.6)	

Abbreviations: CAC, coronary artery calcification.

[a]Illness Risk is defined as intensive care unit admission, invasive ventilation, and death.

[b]Positive Illness Risk Score = high-risk group (illness risk score of ≥ 40.4%).

RESULTS

Demographic Characteristics

The study cohort consisted of 238 patients hospitalized with active COVID-19 who underwent chest CT during hospitalization and had laboratory testing sufficient to calculate the COVID-GRAM Score.

Table 1 summarizes the demographic characteristics of the study population. The mean age was 64 [SD, 15] years. Among the 238 participants, the distribution by sex was nearly even, with 110 females (46.2%). Most participants were non-Hispanic (96.2%) and identified as White (70.9%). Analysis of demographic variables revealed no statistically significant differences in age, sex, ethnicity, race, or marital status between patients admitted to the ICU and those not admitted. However, employment status was significantly associated with ICU admission, with 81% of patients

admitted to the ICU being unemployed compared with 61% of patients not admitted to the ICU ($P < .01$). Patients admitted to the ICU also had a higher mean number of comorbidities (mean, [SD], 3.76 [1.50] vs 3.08 [1.66]; $P < .01$).

COVID-GRAM Score and Coronary Artery Calcification

Table 2 summarizes the study population's COVID-GRAM scores, illness risk scores, CAC severity, and composite scores. The mean COVID-GRAM Score was 155 [SD, 44.9], and the mean illness risk score was 53.9 [SD, 31.1]. Participants admitted to the ICU exhibited higher mean COVID-GRAM Scores (168 [45.4] vs 150 [44.0]) and illness risk score (62.7 [27.7] vs 51 [31.7]) than patients not admitted to the ICU ($P = .01$ for both comparisons).

Among COVID-GRAM Score-related variables, patients admitted to the ICU had higher neutrophil-to-lymphocyte ratios (14.4 [18.8] vs 8.50 [7.83]) and higher lactate dehydrogenase levels (472 [188] vs 369 [164]) than patients not admitted to the ICU ($P < .01$ for all). Hemoptysis, chest radiograph abnormalities, dyspnea, loss of consciousness, cancer history, and direct bilirubin levels did not differ significantly between the groups.

ICU admission was associated with positive CAC findings, particularly severe CAC. Among patients admitted to the ICU, 18.6% had severe CAC compared with 5.6% patients not admitted to the ICU ($P < .01$) (Table 2). Likewise, any CAC was positively associated with ICU admission. Although 42.9% of the study population had any CAC, 54.2% of patients requiring ICU admission had CAC ($P = .04$). However, the association was not statistically significant when moderate-to-severe or severe CAC was compared with non or mild CAC ($P = .22$).

To assess whether combining the COVID-GRAM Score and CAC would better predict outcomes, 3 composite variables were evaluated. Composite 1 (any CAC and a positive illness risk score) was positive in 50.8% of ICU-admitted patients compared with 30.2% of patients not admitted to the ICU ($P < .01$). Likewise, Composite 3 (severe CAC and a positive illness risk score) was positive in 18.6% of ICU-admitted patients compared with 5% of patients not admitted to the ICU ($P < .01$). There was no statistically significant association between Composite 2 (moderate-to-severe CAC and a positive illness risk score) and ICU admission ($P = .22$).

Table 3. Sensitivity, Specificity, and AUC Analysis

Variable		ICU (Yes/No)		Sensitivity	Specificity	AUC
Illness risk score[a]		Positive	Negative	0.8	0.41	0.61
	Positive	47	105			
	Negative	12	74			
Any CAC (mild/moderate/severe)		Positive	Negative	0.54	0.61	0.58
	Positive	32	70			
	Negative	27	109			
Moderate-to-severe CAC		Positive	Negative	0.27	0.8	0.54
	Positive	16	35			
	Negative	43	144			
Severe CAC		Positive	Negative	0.19	0.94	0.57
	Positive	11	10			
	Negative	48	169			
Composite 1[b]		Positive	Negative	0.51	0.7	0.6
	Positive	30	54			
	Negative	29	125			
Composite 2[b]		Positive	Negative	0.27	0.84	0.55
	Positive	16	29			
	Negative	43	150			
Composite 3[b]		Positive	Negative	0.19	0.95	0.57
	Positive	11	9			
	Negative	48	170			

Abbreviations: AUC, area under the receiver operating characteristic curve; ICU, intensive care unit; CAC, coronary artery calcification.

Note: positive = yes; negative = no.

[a]Positive illness risk score = ≥ 40.4%; negative illnes risk score = 1.7% to <40.4%.

[b]Composite 1 (any CAC and positive illness risk score); Composite 2 (moderate-to-severe CAC and positive illness risk score); Composite 3 (severe CAC and positive illness risk score).

Sensitivity, Specificity, and AUC analysis

Table 3 summarizes the sensitivity, specificity, and the area under the receiver operating characteristics curve (AUC) for the COVID-GRAM Score, CAC categories and composite. ROC analysis is a valuable tool for assessing the ability of index tests to accurately diagnose diseases or conditions. The AUC was selected as the primary metric because it summarizes overall discriminatory performance across all possible thresholds.[12] An AUC score of 0.50 indicates that a test's predictive ability is no better than chance, whereas values above 0.80 generally considered clinically useful.[12]

Among the 238 patients analyzed, AUC values were close to 0.50 for all predictors evaluated, including the illness risk score and all CAC levels. As shown in the Figure, the AUC was 0.61 for the illness risk score, 0.58 for any CAC, 0.54 for moderate-to-severe CAC, and 0.57 for severe CAC. Although the illness risk score had the highest AUC (0.61), its performance was not significantly different from that of the CAC-based measures.

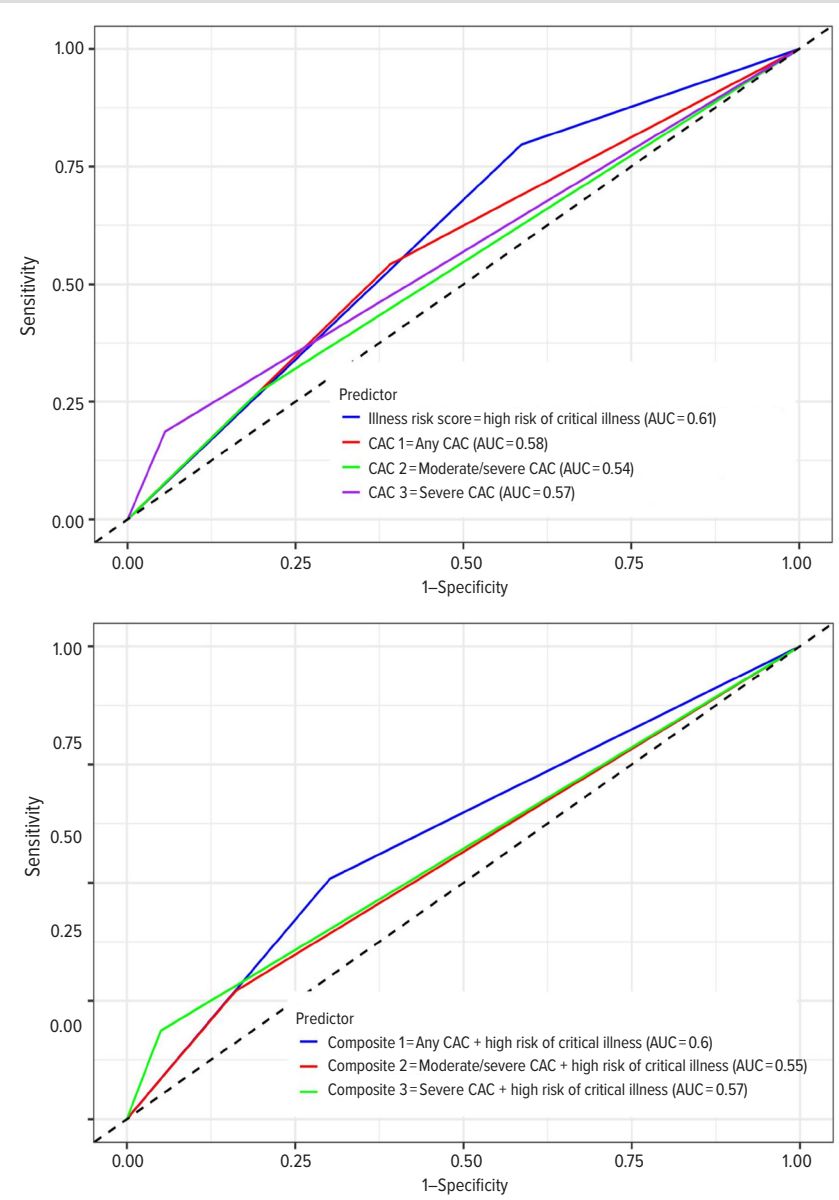
Composite scores did improve predictive performance. The AUC was 0.6 for Composite 1 (any CAC and positive illness risk score), 0.55 for Composite 2 (moderate-to-severe CAC and positive illness risk score), and 0.57 for Composite 3 (severe CAC and positive illness risk score).

DISCUSSION

At a single US academic medical center, the COVID-GRAM Score, incidental CAC identified on CT chest, and their composite measures demonstrated limited discrimination for predicting ICU-level care among hospitalized patients with COVID-19 and no prior clinical coronary artery disease. AUC values ranged from 0.54 to 0.61. Although severe CAC demonstrated high specificity (94%), its low sensitivity limited its utility as a stand-alone predictor. Nevertheless, severe CAC may have value for identifying a small subset of patients at higher risk for ICU admission. The novelty in this study lies in its direct comparison of these 2 risk stratification tools and its evaluation of whether a combining them improves prediction of ICU admission.

Although several comparisons were statistically significant in our cohort, including higher COVID-GRAM and illness risk scores, higher neutrophil-to-lymphocyte ratios, higher lactate dehydrogenase levels, and a greater prevalence of severe CAC and any CAC among ICU-admitted patients, overall discrimination for ICU admission remained poor. AUC values were 0.61 for the illness risk score, 0.58 for any CAC, 0.54 for moderate-to-severe CAC, 0.57 for severe CAC, and 0.60, 0.55, and 0.57 for the 3 composite measures, respectively. These findings are not contradictory. Whereas *P* values from group comparisons test whether mean or proportion differences exist between groups, the AUC assesses how effectively a measure distinguishes individual patients by risk across the sample. In our sample of 238 patients, modest differences between groups were sufficient to yield statistically significant *P* values but did not translate into clinically meaningful discrimination.

Figure. ROC Curves With Binary Outcome Intensive Care Unit (yes/no)



Abbreviations: AUC, area under the receiver operating characteristics curve; CAC, coronary artery calcification; ROC, receiver operating characteristic.

The operating characteristics shown in Table 3 further illustrate this distinction. Predictors with more specific thresholds, such as severe CAC and Composite 3 (specificity, 0.94-0.95; sensitivity, 0.19), identified a relatively small subset of higher-risk patients but failed to detect many ICU admissions. In contrast, the illness risk score (sensitivity, 0.80; specificity, 0.41) identified more patients who required ICU care but produced a substantial number of false-positive results. Accordingly, statistically significant associations should be interpreted as evidence of group-level differences rather than evidence of strong predictive performance. Taken together, the AUC, sensitivity, and specificity findings do not support the use of the COVID-GRAM Score, CAC, or their composite measures alone for triage or prognostication in this setting.

Our findings are consistent with those of Al Hassan et al,[13] who evaluated the COVID-GRAM Score, CALL score, and a nomogram in a multicenter study in the United Kingdom. The reported AUC values were 0.636, 0.500, and 0.628, respectively. The authors attributed the low predictive power of these tools to differences in the patient populations in the United Kingdom and

China. Similarly, the mean age of patients in our study was 63.5 years [SD, 14.8], compared with 48.9 years [15.7] in the original derivation cohort. The outcome of COVID-19 infection is also strongly influenced by underlying comorbidities.[14] In the cohort used to develop the COVID-GRAM Score, 75% of patients had no comorbid conditions, and only 2.5% had 3 or more comorbidities.[11] In contrast, participants in our study had a mean of 3.25 [1.65] comorbidities. These differences likely reduced the generalizability and performance of the COVID-GRAM model in our population.

Multiple previous studies have reported an association between CAC and adverse COVID-19 outcomes, particularly mechanical ventilation and mortality.[10,15,16] Most of these studies were conducted early in the pandemic, outside the United States, and over relatively short study periods when treatment options were limited.[10,15,16] The RECOVERY trial and CoDEX trial demonstrated improvement in mortality associated with dexamethasone in patients with severe COVID-19, leading to changes in treatment protocols.[17,18] Our study spanned July 2020 through July 2021, a period during which treatment strategies evolved substantially. These changes in treatment practices may partially explain the differences in CAC performance observed between our study and earlier reports.

The original study by Kotlo et al[1] analyzed the same patient population and found positive associations between CAC and ICU admission, mechanical ventilation, and mortality. Our analysis was restricted to the subset of patients with available lactate dehydrogenase data, resulting in the exclusion of 226 patients and reducing statistical power. This reduction in sample size may have altered the observed relationships. In addition, comparison of our cohort with the original Chinese derivation cohort highlights the differences in clinical practice patterns. Lactate dehydrogenase was obtained in the Chinese cohort but was not consistently measured in our institution's patient population.[11]

A strength of this study is the inclusion of patients hospitalized over a 12-month period, with a relatively even distribution of men and women. The study also captured patients treated later in the pandemic, when treatment options had become more standardized.

Limitations

A limitation of this study is that it included only patients who underwent nongated chest CT and had the complete laboratory data required to calculate a COVID-GRAM Score. These inclusion criteria may have selected for a sicker patient population. In addition, they resulted in the exclusion of a large subset of eligible patients, reducing the final sample size to 238 and limiting the representativeness of the cohort.

Another limitation is the assessment of CAC using nongated chest CT to diagnose and assess COVID-19 severity and a semiquantitative classification of none, mild, moderate-to-severe, and severe CAC rather than the quantitative Agatston scoring. This approach is potentially subjective and may vary among radiologists. Furthermore, only a limited number of studies have validated CAC assessment against the Agatston score, which remains the reference standard.[7,19]

The study may also have been underpowered. The calculated sample size required to achieve a power of 80% and acceptable AUC values was 252 participants. Because the final sample included only 238 participants, the possibility of a type II error cannot be excluded, meaning that potentially important associations may have gone undetected.[20,21] Accordingly, these findings should be considered preliminary and warrant confirmation in larger, prospective, multicenter studies.

CONCLUSIONS

The presence of incidental severe CAC in patients with COVID-19 and no prior history of clinical coronary artery disease may indicate an increased likelihood of requiring ICU-level care and should prompt heightened clinical awareness. However, our finding also highlight the limitations of the COVID-GRAM Score for predicting severe COVID-19 illness necessitating ICU admission. Because the score was developed and validated in specific patient populations, its performance may not generalize to other clinical settings. In our cohort, a high COVID-GRAM Score demonstrated limited ability for predicting ICU admission, and CAC did not outperform the COVID-GRAM Score. Furthermore, combining CAC with the COVID-GRAM Score did not meaningfully improve predictive performance. Accordingly, these tools should be used cautiously and should not serve as stand-alone determinants of clinical decision-making. Further large-scale, prospective, multicenter studies are needed to better define the role of CAC and COVID-19 risk prediction models in identifying patients at risk for severe illness.

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