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Coronary artery calcification in COVID-19 patients: an imaging biomarker for adverse clinical outcomes

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ABSTRACT

Background: Recent studies have demonstrated a complex interplay between comorbid cardiovascular disease, COVID-19 pathophysiology, and poor clinical outcomes. Coronary artery calcification (CAC) may therefore aid in risk stratification of COVID-19 patients.

Methods: Non-contrast chest CT studies on 180 COVID-19 patients ≥ age 21 admitted from March 1, 2020 to April 27, 2020 were retrospectively reviewed by two radiologists to determine CAC scores. Following feature selection, multivariable logistic regression was utilized to evaluate the relationship between CAC scores and patient outcomes.

Results: The presence of any identified CAC was associated with intubation (AOR: 3.6, CI: 1.4–9.6) and mortality (AOR: 3.2, CI: 1.4–7.9). Severe CAC was independently associated with intubation (AOR: 4.0, CI: 1.3–13) and mortality (AOR: 5.1, CI: 1.9–15). A greater CAC score (UOR: 1.2, CI: 1.02–1.3) and number of vessels with calcium (UOR: 1.3, CI: 1.02–1.6) was associated with mortality. Visualized coronary stent or coronary artery bypass graft surgery (CABG) had no statistically significant association with intubation (AOR: 1.9, CI: 0.4–7.7) or death (AOR: 3.4, CI: 1.0–12).

Conclusion: COVID-19 patients with any CAC were more likely to require intubation and die than those without CAC. Increasing CAC and number of affected arteries was associated with mortality. Severe CAC was associated with higher intubation risk. Prior CABG or stenting had no association with elevated intubation or death.

1. Introduction

As the global coronavirus disease (COVID-19) pandemic continues, risk stratification for infected patients has become increasingly important to decrease morbidity and mortality. Recent studies have demonstrated a complex interplay between cardiovascular disease, COVID-19 pathophysiology, and poor clinical outcomes [1–6]. Imaging biomarkers such as coronary artery calcium (CAC) score have an established role in long-term cardiovascular event risk stratification but might also provide important prognostic information and

Abbreviations: COVID-19, coronavirus disease 2019; CAC, coronary artery calcium; NCCT, non-contrast computed tomography; ECG, electrocardiogram; SAPT, single antiplatelet therapy; DAPT, dual antiplatelet therapy; OAC, oral anticoagulant; AKI, acute kidney injury; VTE, venous thromboembolism; COPD, chronic obstructive pulmonary disease; UOR, unadjusted odds ratio; AOR, adjusted odds ratio.

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pathophysiologic insights in patients acutely ill with COVID-19.

CAC score is an independent predictor of cardiovascular events [7,8]. Visual CAC scoring on non-electrocardiogram (ECG)-gated, non-contrast chest CT studies (NCCT) is a well-established, efficient, and reproducible surrogate for quantitative analysis, demonstrating strong association with the widely utilized Agatston score, without the need for an additional dedicated ECG-gated cardiac CT study or computational software [9-11]. NCCTs are sometimes obtained in COVID-19 patients to assess the extent of pulmonary disease, monitor disease progression, and to investigate the presence of disease complications [12]. NCCTs have also been widely used in some countries for rapid detection of suspected COVID-19 and is also often performed as a diagnostic supplement to PCR testing in other countries such as the United States [13,14]. Mining of these studies for imaging biomarkers may provide further insight into the disease process from both pathophysiologic and clinical perspectives, performed in the context of a pandemic that has necessitated efficient use of often limited healthcare resources.

In this study, we examine the association between visual CAC scoring on NCCTs in COVID-19 patients with adverse clinical outcomes. In addition, we perform a comparative analysis of CAC severity with respect to adverse outcomes to a variety of clinical, imaging, and laboratory factors. We hypothesize that increasing severity and extent of CAC are independent predictors of poor outcomes in COVID-19.

2. Materials and methods

This is an IRB-approved retrospective cohort study of 180 patients ≥ age 21 admitted from March 1, 2020 to April 27, 2020 within a large urban multicenter system positive for COVID-19 by reverse transcription polymerase chain reaction and underwent NCCT.

2.1. Inclusion criteria for patients

Using an institutional COVID-19 dataset, 198 admitted patients ≥ the age 21 with NCCT within a 3-month period prior to and after admissions were identified. Patients with prior coronary artery bypass graft (CABG) surgery or coronary arterial stenting, determined by radiologist suspicion with electronic medical record (EMR) confirmation, were excluded from CAC scoring but were included in outcomes analysis. NCCTs on which at least one radiologist suspected coronary stenting that could not be confirmed or repudiated by EMR were excluded (n = 8). NCCTs deemed too limited by motion artifact for adequate CAC assessment by at least one radiologist were excluded (n = 7). After exclusions, 180 patients were included for outcomes analysis (Fig. 1).

2.2. Clinical data collection

Patient information was collected from the EMR. Demographic variables included age, gender, self-reported race and ethnicity. Clinical variables included past medical history (as shown in Table 1), body mass index (BMI), smoking history, echocardiography results, laboratory variables including troponins, and selected outpatient medications (statins, antiplatelet regimen, anticoagulant regimen). Antithrombotic therapy was classified as single antiplatelet (SAPT), dual antiplatelet (DAPT), or oral anticoagulant (OAC) [14]. The statin regimen was categorized as combined low/moderate or high intensity following available ACC guidelines [16-18]. The highest available D-dimer level during admission was recorded (D-dimer level > 1 μg/mL was considered elevated) [19,20]. Echocardiography results were obtained from EMR. End results of every admission (discharge or death) were recorded for every encounter.

2.3. Imaging data collection

All NCCTs contained 1-mm-thick slices. They were obtained from five sites in New York City. In Brooklyn, 108 patients were scanned on Aquilion PRIME (Toshiba, Tokyo, Japan). In Manhattan, 39 patients were scanned on Somatom Definition AS+ (Siemens, Munich, Germany), 14 patients were scanned on iCT 256 (Philips, Amsterdam, The Netherlands), and 4 patients were scanned on Revolution EVO (General Electric, Chicago, USA). In Queens, 15 patients were scanned on Revolution HD (General Electric, Chicago, USA).

2.4. Imaging analysis

Two fellowship-trained cardiothoracic radiologists (Y.S.G. and J.C.; total experience of 12 years) with extensive experience in CAC assessment independently scored each NCCT on soft tissue window of a standard PACS workstation, blinded to patient histories other than COVID-19 positivity. Visual assessment of CAC was performed according to an established ordinal scoring method [21]. Each of the four main coronary arteries was identified (left main, left anterior descending, left circumflex, and right coronary arteries). Calcium extent was scored as 0, 1, 2, or 3 (Fig. 2). A score of 1 is defined as involvement of less than one third of the vessel length; 2 as involvement of one third to two thirds of the vessel length; 3 as greater than two thirds of the vessel length. These scores were summed to obtain a total ordinal score of 0–12 for each scan. The total scores were categorized as absent CAC for score 0, mild for score 1–3, moderate for a score 4–5, and severe for score ≥ 6.

When patients had changes indicative of prior coronary artery bypass graft (CABG) surgery or stent placement, confirmed on EMR, CAC scoring was not performed.

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Fig. 1. Study flow diagram.
This diagram demonstrates how we arrived at the total number of patients included in the outcomes analysis for our retrospective cohort study.
statistical analysis

Weighted Cohen’s kappa coefficient was used to assess radiologists’ agreement in scoring. For individual vessels, stent and CABG cases were excluded in this calculation, due to these being unscorable. The mean of possible in multivariable analysis, missing BMI (11/180, 6.1%) were excluded in this calculation, due to these being unscorable. The mean of

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analysis was completed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Population characteristics, comorbidities, and medications

A total of 180 patients were included in the analysis (median age 68 [interquartile range (IQR) 59–80]; 46% female). Fifty-four out of 180 (30%) patients reported being current or former smokers, and 68/169 (40%) were obese or morbidly obese (as defined by BMI > 30). The most common comorbidities were hypertension (60/180; 33%) and diabetes mellitus type II (42/180; 23%). Admitted patient demographics and past medical histories in relation to intubation and expiration are displayed in Table 1. Encounter location is described in Supplementary Table 1.

Fourteen patients out of 180 (8%) were found to be on DAPT, 49/180 (27%) were on SAPT, 22/180 (12%) on OAC, and 95/180 (53%) were on no antithrombotic regimen. Thirty-one out of 180 patients (17%) were on high intensity statin therapy prior to admission, 55/180 (31%) were on low/moderate intensity statin therapy, and 94/180 (52%) were not on any statin regimen. Of the patients with stents and/or CABG, 20/22 (91%) were on a statin regimen, and 21/22 (95%) were on an antithrombotic regimen. Of the patients with CAD, 9/25 (36%) were found to have stents and/or CABG. Admitted patient CAC scores, echocardiography findings, and laboratory parameters in relation to intubation and expiration are shown in Table 2. Additional data relating lab and echocardiography findings in relation to the outcomes of interest are provided in Supplemental Table 1.

3.2. Coronary artery calcium scores

One-hundred-eighty NCCT scored by the two radiologists had almost perfect concordance based on category (Kappa 0.84). Concordance scores for individual vessels were: left main coronary artery (Kappa 0.61), left anterior descending artery (Kappa 0.79), left circumflex coronary artery (Kappa 0.68), and right coronary artery (Kappa 0.80). Concordance of number of calcified vessels, calculated by summing the number vessels with greater than 0 CAC score, was substantial (Kappa 0.82) as was the total summed score (Kappa 0.73).

3.3. Clinical outcomes

Fifty-four patients (30%) were intubated during their admission, 59 (33%) died, and 95 (86%) had elevated D-dimer (as defined by >1 μg/L). Results of feature selection for the multivariable analysis involving CAC categories showing the relative calculated importance of different features is displayed in Figs. 3 and 4. Every category of CAC score was associated with increased odds of intubation in reference to absence of

Table 2

| CAC distribution | Left main | Left anterior descending | Left circumflex | Right coronary |
|------------------|-----------|--------------------------|-----------------|---------------|
| Reader 1         | 31.0*     | 60.8 (96)                | 32.5 (51)       | 42.4 (67)     |
|                  | (49)      |                          |                 |               |
| Reader 2         | 44.3      | 62.0 (98)                | 44.3 (70)       | 45.6 (72)     |
|                  | (70)      |                          |                 |               |
| Kappa            | 0.61      | 0.79                     | 0.68            | 0.80          |

Data is provided in percentages, with number of patients in parenthesis.
CAC (mild - AOR: 3.3, CI: 1.1–9.8, moderate - AOR: 6.5, CI: 1.9–24, severe - AOR: 4.0, CI: 1.3–13). A severe CAC score was associated with increased odds of mortality (AOR: 5.1, CI: 1.9–15). Additionally, in the model utilizing CAC category, morbid obesity was associated with increased risk of both intubation (AOR: 3.3, CI: 1.1–10) and mortality (AOR: 5.4, CI: 1.8–17). No statistically significant association was found between the category of patients with stent and/or CABG and the outcomes of intubation (AOR: 1.9, CI: 0.4–7.7) or mortality (AOR: 3.4, CI: 1.0–12). For complete univariable and multivariable logistic regression analysis results, see Table 3. Increasing CAC score was found to be associated with mortality (UOR: 1.2, CI: 1.0–1.3), but not intubation (UOR: 1.0, CI: 0.9–1.1). Increasing number of vessels with calcification was associated with mortality (UOR: 1.3, CI: 1.02–1.6), but not intubation (UOR: 1.0, CI: 0.8–1.2). There was no association between statin regimen and antithrombotic regimen and the outcomes of interest (Table 3).

3.4. Secondary outcomes

Both mild/moderate (AOR: 5.7, CI: 1.1–40) and severe (AOR: 11, CI: 1.4–124) CAC score categories were found to be associated with an elevated D-dimer. No association was found between CAC categories and score in relation to acute kidney injury (AKI), elevated troponin, and elevated liver function tests. Patients on higher intensity statins had a higher CAC score (none - median 0.75 [IQR 0.00, 3.50], low/moderate - median 3.50 [IQR 1.38, 5.75], high - median 5.50 [IQR 2.75, 8.00], p < 0.001). Elevated D-dimer was not associated with presence or absence of stents or history of CABG (AOR: 5.0, CI: 0.4–78).

4. Discussion

In this retrospective analysis, we studied the relationship between the presence and extent of CAC with adverse outcomes in COVID-19
patients. Our results indicate that COVID-19 patients with any degree of CAC were more likely to require intubation or expire than those without CAC. Higher CAC score was associated with increased mortality. Pa-

Table 3
Risk of intubation and death in admitted patients with COVID-19. Model covariates for the adjusted model were chosen through feature selection

| Variable                      | Intubation | Death |
|-------------------------------|------------|-------|
|                               | Unadjusted odds ratio | Adjusted odds ratio for any calcification | Unadjusted odds ratio | Adjusted odds ratio for any calcification |
| Age                           | 0.97 (0.95-0.99) | 0.96 (0.93-0.99) | 1.0 (1.0-1.04) | – |
| Race                          | Reference | – | Reference | – |
| Black                         | 2.0 (0.89-4.5) | – | 1.0 (0.49-2.2) | – |
| Other/unknown                 | 1.9 (0.83-4.6) | – | 0.66 (0.29-1.5) | – |
| Sex                           | Reference | – | Reference | – |
| Male                          | Reference | – | 1.0 (0.54-1.9) | – |
| Female                        | 0.94 (0.49-1.8) | – | – | – |
| BMI cutoffs (kg/m²)           | Reference | Reference | Reference | Reference |
| Normal (< 25)                 | Reference | – | – | – |
| Overweight (25-30)            | 2.4 (0.97-5.9) | 2.5 (0.98-6.8) | 1.5 (0.61-3.4) | – |
| Obese (31–40)                 | 2.5 (1.1-6.2) | 2.0 (0.8-5.3) | 1.9 (0.8-2.4) | 2.4 (1.0-6.1) |
| Morbidly obese (>40)          | 4.3 (1.5-13) | 3.3 (1.1-10) | 3.5 (1.3-9.7) | 5.4 (1.8-16.9) |
| Comorbidities                 | – | – | – | – |
| COPD                          | 0 | – | 1.2 (0.25-5.3) | – |
| HTN                           | 1.6 (0.82-3.1) | – | 1.3 (0.67-2.5) | – |
| DM                            | 0.91 (0.41-1.9) | – | 1.0 (0.49-2.1) | – |
| AFIB                          | 0 | – | 1.6 (0.30-7.3) | – |
| Cancer                        | 0.48 (0.15-1.3) | – | 0.84 (0.33-2.0) | – |
| CKD                           | 2.0 (0.90-4.6) | – | 2.8 (1.3-6.4) | 2.5 (1.1-5.6) |
| HF                            | 2.2 (0.85-5.4) | – | 1.5 (0.58-3.7) | – |
| CAD                           | 0.9 (0.3-2.2) | – | 1.8 (0.7-4.1) | – |
| Presence of calcification     | – | – | – | – |
| No calcification              | Reference | – | Reference | – |
| Any calcification             | 1.4 (0.67-2.9) | 3.6 (1.4-9.6) | 3.5 (1.60-8.6) | 3.2 (1.4-7.9) |
| Number of vessels involved    | 1.0 (0.8-1.2) | – | 1.3 (1.02-1.6) | – |
| CAC score categories          | – | – | – | – |
| Absent                        | Reference | – | Reference | – |
| Mild                          | 1.6 (0.67-4.0) | 3.3 (1.1-9.8) | 3.0 (1.1-8.3) | 3.0 (1.1-8.9) |
| Moderate                      | 2.2 (0.79-6.4) | 6.5 (1.9-24) | 2.9 (0.91-9.2) | 3.2 (0.97-11) |
| Severe                        | 1.2 (0.46-3.0) | 4.0 (1.3-13) | 4.4 (1.7-12.3) | 5.1 (1.9-15) |
| Stent/CABG                    | 0.65 (0.16-2.1) | 1.9 (0.4-7.7) | 3.7 (1.2-12) | 3.4 (1.0-12) |
| CAC continuous score          | 1.0 (0.90-1.1) | – | 1.2 (1.02-1.3) | – |
| Antithrombotic regimen        | – | – | – | – |
| None                          | Reference | – | Reference | – |
| SAPT                          | 0.65 (0.30 to 1.4) | – | 1.6 (0.79-3.3) | – |
| DAPT                          | 0.49 (0.11-1.7) | – | 0.17 (0.01-0.90) | – |
| OAC                           | 0.40 (0.11-1.2) | – | 1.01 (0.35-2.7) | – |
| Statin regimen                | – | – | – | – |
| None                          | Reference | – | Reference | – |
| Low/moderate                  | 0.69 (0.32-1.4) | – | 1.2 (0.57-2.3) | – |
| High                          | 0.83 (0.33-2.0) | – | 0.71 (0.27-1.7) | – |

Coronary artery calcium score is expressed by categories and as a continuous score. Data in parenthesis are 95% confidence intervals. BMI = body mass index; COPD = chronic obstructive pulmonary disease; HTN = hypertension; DM = diabetes mellitus; CKD = chronic kidney disease; HF = heart failure; CAD = coronary artery disease; AFIB = atrial fibrillation; CAC = coronary artery calcium; CABG = coronary artery bypass grafting. Mild and moderate groups for CAC were combined for the analysis relating to elevated D-dimer as an outcome due to low counts in the moderate group.

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cardiovascular disease and subsequent mixed shock, as suggested by recent literature [27,28]. It may also point to underlying chronic inflammation that predisposes to atherosclerotic disease and to acute proinflammatory states such as the cytokine storm.

Although studies have found that COVID-19 patients with CAD are more likely to have myocardial injury, we did not find a similar association in patients with a pre-admission diagnosis of CAD (25/180), which may be attributable to under-diagnosis given the large group of patients with visually moderate or severe CAD (65/180) [1,29]. We did not find a significant association between CAC and troponin elevation, although this may be secondary to relatively small sample size. The association between CAC and mortality in our study in the absence of clinical evidence of myocardial injury suggests the predictive value of CAC may not be limited to the cardiac domain, reflecting host propensity for widespread proinflammatory response and endothelial
dysfunction. In autopsy studies of COVID-19 patients, endothelial injury, perivascular inflammation, and/or microthrombosis have recently been implicated as dominant findings in multiple organs, including the lungs, brain, kidneys, skin, and gastrointestinal tract [30–32].

We found no statistically significant association between CAGB or stent placement and intubation or death in our cohort. Recent literature suggests that hospitalized COVID-19 patients on anticoagulation have reduced mortality risk while those on statins may benefit [29,33]. We hypothesized that the CAGB/stent patients may have benefited from such medications as they are more likely to be on them. However, upon analysis of our entire cohort, we found these therapies did not confer any advantage. One possibility is that CAGB/stented patients benefited from surgical/procedural management of obstructive CAD in this regard.

In keeping with prior studies, our data demonstrates a positive association of intensity of statin regimen with CAC scores [34,35].

Our results indicate a significant role for assessing CAC severity and extent in COVID-19 patients. Visual CAC scoring demonstrated almost perfect interobserver agreement in our study (Kappa = 0.84), which is in keeping with existing literature (kappa was as high as 0.95 in the previously referenced study by Azour et al.) [21]. As such, visual CAC scoring is a reliable method that can facilitate prognostication in COVID-19 patients. Additionally, our study supports the feasibility of CAC assessment on almost all COVID-19 patients who undergo non-ECG-gated NCCTs around the time of illness.

NCCTs are sometimes performed on hospitalized COVID-19 patients for various reasons; therefore, visual CAC scoring does not require additional imaging assessment but can provide useful prognostic data [36]. Although CAC is an established imaging marker for predicting cardiovascular event risk, CAC reporting incidence may be as low as 1% [36,37]. CAC on NCCT may be the first evidence of undiagnosed CAD and may be a more objective and dependable means of rapid risk stratification in COVID-19 patients, unaffected by confounding variables such as recall bias that may occur during history taking. We recommend radiologists report CAC in all COVID-19 patients to best guide clinical management.

Limitations of this study include its retrospective nature, which may introduce observer bias in CAC assessment. Our cohort was limited to patients who had a NCCT, which may impart selection bias and may not represent the full array of associations of CAC with COVID-19 outcomes. Furthermore, as described previously, patients with NCCT within a 3-month period prior to and after admission were included, which may have resulted in higher relative inclusion of patients who survived. Future investigation may incorporate a cohort with more diverse imaging to determine an association of CAC with other adverse events, including VTE, stroke, and bowel ischemia.

5. Conclusion

Visual CAC scoring on routine NCCTs in hospitalized COVID-19 patients is a rapid and reproducible imaging biomarker that may provide an independent assessment of risk of intubation and death, with those having severe CAC at higher risk. Patients treated with CAGB/stents did not incur a similar risk, possibly reflecting a combination of treated CAD and medical therapy. Assessing CAC severity on NCCTs imparts valuable information regarding risk prognostication and may guide management in COVID-19 patients.

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Consent

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