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Research paper

Coronary artery calcification as a predictor of adverse outcomes in patients hospitalized with COVID-19

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ABSTRACT

Background: Subclinical coronary artery calcification (CAC) is a risk factor for adverse cardiovascular events, but studies investigating its association with outcomes in hospitalized patients with COVID-19 are limited.
Methods: This was a retrospective study of 457 patients without history of clinical coronary artery disease (CAD) who underwent chest CT imaging during COVID-19 hospitalization at MCW/Froedtert-affiliated hospitals from July 1, 2020 to July 1, 2021. Visually estimated CAC (yes/no) and CAC burden (none/mild/moderate/severe) were recorded from radiology reports. Unadjusted and adjusted regression models were used to assess associations between CAC and hospital length of stay (LOS), ICU admission, mechanical ventilation, and mortality.
Results: The mean age was 63.1 ± 15.3 years. Presence of CAC was associated with mechanical ventilation ($p = 0.01$), ICU admission ($p = 0.02$), in-hospital or 30-day mortality ($p < 0.01$), and hospital LOS ($p < 0.001$). Compared to no CAC, hospital LOS was increased for mild ($p = 0.01$) and severe CAC ($p = 0.02$) after adjustment for covariates. Severe CAC was also associated with increased ICU admission (OR 3.97; $p = 0.002$) and mechanical ventilation (OR 3.08; $p = 0.03$) after adjustment. In unadjusted analysis, in-hospital or 30-day mortality increased with magnitude of CAC severity, with HR 2.43 ($p = 0.003$) for mild and HR 3.70 ($p = 0.002$) for severe CAC. However, associations with mortality were not significant after adjustment.
Conclusions: CAC is associated with increased ICU admission, mechanical ventilation, hospital LOS, and in-hospital or 30-day mortality for patients hospitalized with COVID-19. Patients with severe CAC, and without clinical history of CAD, represent a high-risk population for morbidity and mortality.

1. Introduction

Coronavirus disease of 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel single-stranded enveloped RNA virus that is thought to invade cells through the angiotensin-converting enzyme 2 (ACE-2) receptor [1,2]. It has affected over 500 million people worldwide and resulted in over 6 million deaths as of May 2022 [3]. The virus has been shown to increase morbidity in those with underlying cardiovascular conditions and can lead to myocardial injury [1,2].

Coronary artery calcification (CAC) can be detected by CT imaging and provides insight into a patient's level of cardiovascular disease risk [4,5]. CAC has been associated with future adverse cardiovascular events and correlates with the extent of CAD [5,6]. Those with no coronary calcification detected have low risk of cardiovascular events and those with severe calcification are at risk for worse clinical outcomes [4]. It is currently recommended to use calcium scoring to improve cardiovascular risk assessment in intermediate-risk patients [7]. The value of CAC testing has been validated in numerous studies and CAC has been shown to be a good predictor of future events in the general population [8]. It has also been shown to provide better risk prediction than factors such as family history of premature heart disease and even some CVD risk calculators [8,9].

There are numerous ways in which CAC is assessed based on computed tomography. CT examinations that are ECG gated minimize motion artifact and provide reproducible CAC scoring when images are reconstructed. For gated CT examinations, the Agatston score is commonly used to quantify extent of calcification and remains the gold standard for CAC scoring [4,8,10]. Routine CT chest scans, such as those performed to diagnose and assess severity of disease in COVID-19, are

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non-ECG gated studies which can provide a visual assessment of CAC (none, mild, moderate, or severe) [10]. The visual estimation of CAC from these scans is still clinically useful and an effective method of assessment as it was tested in the National Lung Cancer Screening Trial (NLST) with good agreement between visual assessment of CAC and Agatston scores [8,10].

In the setting of COVID-19 there are few studies that have looked at CAC and association with outcomes in hospitalized patients. These studies are limited by older or predominantly male cohorts, small sample sizes, and being early-pandemic studies which limits assessment of mortality and other adverse outcomes given that treatment was not well-defined at that time [11–15]. The objective of our study was to see if qualitative assessment of CAC from chest CT imaging can predict risk of adverse outcomes in patients without a prior clinical history of CAD who are hospitalized with COVID-19.

2. Methods

This retrospective cohort study was approved by the institutional review board at the Medical College of Wisconsin. The need for individual informed consent was waived.

2.1. Inclusion and exclusion criteria

Patients at least 18 years old without prior coronary artery disease (prior MI, PCI, or CABG) who were hospitalized with an active COVID-19 infection from July 1, 2020 to July 1, 2021 at MCW/Froedtert-affiliated hospitals were included. The infection must have been confirmed with a RT-PCR test done prior to or during the hospitalization. Of these patients, only those who underwent a CT chest during hospital admission for COVID-19 were included.

The study excluded individuals <18 years old, those without a COVID-19 diagnosis, patients who previously tested positive or were diagnosed with COVID-19 but without active infection during the hospital stay, patients with history of coronary artery disease, and patients who did not undergo a CT chest during the hospitalization. For some CT chest scans, the interpreting radiologist only read presence of coronary artery calcification without grading severity of the calcification. These patients (n = 30) were included in the CAC versus no CAC analyses but excluded from the analyses that were based on CAC severity.

2.2. Study approach and data collection

The initial list of patients for chart review was obtained using the Clinical Research Data Warehouse (CRDW) tools I2B2 and Honest Broker provided by our institution's Clinical and Translational Science Institute (CTSI). The sample included 457 patients hospitalized with COVID-19 at MCW/Froedtert-affiliated hospitals who underwent CT chest scans during admission and did not have a prior history of coronary artery disease.

Data was collected via manual chart review of patient medical records in Epic and utilization of the CRDW tools. The coronary artery calcification variable was recorded by opening the CT chest report from the hospital admission and recording the radiologist's reading from the coronary artery section of the report. Of the 457 CT scans, 448 were CT angiography of the chest, 7 were CT chest without contrast, and 2 were CT chest with contrast. CAC, in general, was read out as none, mild, moderate, or severe calcification. This fully qualitative assessment was performed by one radiologist who read the scan. Results from only one chest CT was recorded per patient. If the patient had multiple chest CT scans during an admission, the most recent CT scan was used. Some patients had consecutive admissions for COVID-19 and these admissions were pooled as one combined admission with hospital length of stay calculated accordingly.

2.3. Statistical analysis

The exposure variable was coronary artery calcification (yes/no and none, mild, moderate, or severe calcification). Outcome variables were mechanical ventilation, hospital length of stay, necessity of ICU care, ICU length of stay, and mortality (in-hospital and combined in-hospital and 30 days afterwards). Covariates included age, sex, race, hypertension, diabetes, CKD, COPD, hyperlipidemia, smoking status, and BMI.

Continuous variables were reported as a mean with standard deviation. Categorical variables were reported as frequency and percentage. Two sample *t*-tests were utilized to assess for differences in continuous variables between patients with and without CAC. Chi-square tests were utilized to compare categorical variables between patients with and without CAC. Further analysis was done based on CAC severity. One-way ANOVA tests were conducted to compare continuous variables among those with no, mild, moderate, or severe CAC. Chi-square tests were utilized to compare categorical variables among those with no, mild, moderate, or severe CAC. If <5 observations were present, a Fisher's exact test was done in place of the chi-square test.

Unadjusted logistic regression was used to assess associations between CAC (binary and 4-level) and the outcomes of mechanical ventilation and necessity for ICU care. Cox proportional hazards models were used to assess associations between both CAC variables and in-hospital and 30-day mortality where time was defined from July 1, 2020 until the date of the specific death outcome (or until July 31, 2020 if alive). Generalized linear regression was used to assess associations between both CAC variables and length of stay outcomes (hospital LOS and ICU LOS). Unadjusted models with statistically significant results were adjusted for covariates (age, sex, race, hypertension, diabetes, CKD, COPD, hyperlipidemia, smoking status, and BMI). All analyses were performed using STATA version 15 and a p-value <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics and CAC

A total of 457 patients who were hospitalized with COVID-19, underwent a CT chest during hospitalization, and did not have a prior history of coronary artery disease were included in this study. Of these patients, 30 had CT scans which read that CAC was present but with undocumented severity. Therefore, for the severity data, a total of 427 patients were included. Baseline characteristics are presented in Table 1 and Table A1. Of the 427 patients, 244 (57.1 %) had no CAC, 102 (23.9 %) had mild, 48 (11.2 %) had moderate, and 33 (7.7 %) had severe CAC (Table A1). The mean age was 63.1 ± 15.3 years with 50.1 % of the patients being male and 49.9 % being female. The mean BMI was 32.9 ± 8.4. Hypertension (60.4 %), smoking (50.8 %), hyperlipidemia (39.4 %), and diabetes (31.1 %) were the most common risk factors (Table 1).

The average age was higher for patients with CAC compared to without ($p < 0.001$). There was a larger proportion of males with CAC compared to without ($p = 0.02$). There were significant differences between race categories for those with CAC compared to without and a larger proportion of non-Hispanic white patients had CAC ($p = 0.01$). There was a higher rate of hypertension ($p < 0.001$), diabetes ($p = 0.02$), CKD ($p = 0.01$), COPD ($p = 0.001$), hyperlipidemia ($p < 0.001$), and smoking ($p = 0.001$) associated with the CAC group compared to those without CAC. Presence of CAC was also associated with a higher rate of mechanical ventilation ($p = 0.01$), requirement of ICU care ($p = 0.02$), mortality in hospital or within 30 days of discharge ($p < 0.001$), and longer hospital length of stay ($p < 0.001$) (Table 1). Similar differences were seen when comparing across CAC severity groups as shown in Table A1.

Table 1
Differences in demographic characteristics, comorbidities, and hospital outcome variables among patients with and without CAC.

	Total (n = 457)	No CAC (n = 244)	CAC (n = 213)	p-value
Age (years)	63.1 ± 15.3	55.8 ± 14.6	71.4 ± 11.3	**<0.001**
Sex (%)				
Male	229 (50.1 %)	110 (45.1 %)	119 (55.9 %)	**0.02**
Female	228 (49.9 %)	134 (54.9 %)	94 (44.1 %)	
Race (%)				
NHW	313 (68.5 %)	151 (61.9 %)	162 (76.1 %)	**0.01**
NHB	112 (24.5 %)	74 (30.3 %)	38 (17.8 %)	
Hispanic	13 (2.8 %)	8 (3.3 %)	5 (2.4 %)	
Other	19 (4.2 %)	11 (4.5 %)	8 (3.8 %)	
BMI (kg/m^2)	32.9 ± 8.4	34.8 ± 8.7	30.7 ± 7.5	**<0.001**
Comorbidities (%)				
Hypertension	276 (60.4 %)	117 (48.0 %)	159 (74.7 %)	**<0.001**
Diabetes Mellitus	142 (31.1 %)	64 (26.2 %)	78 (36.6 %)	**0.02**
CKD	57 (12.5 %)	21 (8.6 %)	36 (16.9 %)	**0.01**
COPD	52 (11.4 %)	16 (6.6 %)	36 (16.9 %)	**0.001**
Hyperlipidemia	180 (39.4 %)	66 (27.1 %)	114 (53.5 %)	**<0.001**
Smoking: current/former	230 (50.8 %)	106 (43.4 %)	124 (59.3 %)	**0.001**
Outcomes				
Hospital length of stay (days)	9.8 ± 10.8	8.0 ± 8.3	11.9 ± 12.8	**<0.001**
Necessity for ICU care (%)	102 (22.3 %)	44 (18.0 %)	58 (27.2 %)	**0.02**
ICU length of stay (days)	13.9 ± 15.1	11.2 ± 10.1	15.9 ± 17.9	0.12
Mechanical ventilation (%)	58 (12.7 %)	22 (9.0 %)	36 (16.9 %)	**0.01**
In-hospital mortality (%)	53 (11.6 %)	18 (7.4 %)	35 (16.4 %)	**0.003**
In-hospital+30-day mortality (%)	64 (14.0 %)	21 (8.6 %)	43 (20.2 %)	**<0.001**

3.2. Hospital length of stay (LOS)

Patients with CAC compared to without CAC had longer hospital LOS in the unadjusted model ($p < 0.001$) and this significance remained after adjustment for covariates ($p = 0.02$; Table A2). Findings were also significant for the different CAC severities, with mild ($p < 0.001$), moderate ($p = 0.02$), and severe ($p < 0.001$) CAC having longer hospital LOS compared to no CAC in the unadjusted model. After adjustment for covariates, mild ($p = 0.01$) and severe CAC ($p = 0.02$) were still associated with a longer hospital LOS compared to no CAC, with the severe group having a higher coefficient of 0.50 (95 % CI 0.10–0.91) compared to the mild group which had a coefficient of 0.35 (95 % CI 0.09–0.60). Age ($p < 0.002$), hypertension ($p = 0.01$), diabetes ($p = 0.04$), and CKD ($p = 0.01$) were independent predictors of hospital LOS in the unadjusted model. After adjustment for covariates, age remained as a significant predictor of hospital LOS ($p = 0.04$) (Table 2).

3.3. ICU care requirement

A total of 102 (22.3 %) patients required ICU care during admission for COVID-19. ICU requirement was higher for those with CAC (27.2 %) compared to without (18.0 %; $p = 0.02$; Table 1). ICU care requirement was significantly different across CAC severity groups ($p < 0.001$) with the no CAC group comprising the lowest proportion (18.0 %) and severe CAC group comprising the highest proportion (48.5 %) of those requiring ICU care (Table A1).

Patients with CAC compared to without CAC had increased ICU care requirement in the unadjusted model (OR 1.70; 95 % CI 1.09–2.65; p =

Table 2
Generalized linear models for hospital length of stay (LOS). Adjusted model corresponds to CAC severity and is adjusted by all listed covariates (age, sex, race, hypertension, diabetes, CKD, COPD, hyperlipidemia, smoking status, and BMI).

	Unadjusted model		Adjusted model	
	Coefficient (95 % CI)	p-value	Coefficient (95 % CI)	p-value
CAC Severity				
None (ref)	–	–	–	–
Mild	0.45 (0.21, 0.69)	**<0.001**	0.35 (0.09, 0.60)	**0.01**
Moderate	0.37 (0.05, 0.69)	**0.02**	0.25 (−0.11, 0.60)	0.17
Severe	0.68 (0.30, 1.06)	**<0.001**	0.50 (0.10, 0.91)	**0.02**
Age	0.01 (0.00, 0.02)	**0.002**	0.01 (0.00, 0.02)	**0.04**
Sex				
Male (ref)	–	–	–	–
Female	−0.19 (−0.38, 0.01)	0.06	−0.16 (−0.36, 0.05)	0.13
Race				
NHW (ref)	–	–	–	–
NHB	0.03 (−0.21, 0.26)	0.82	0.08 (−0.16, 0.33)	0.52
Hispanic	0.19 (−0.39, 0.78)	0.52	0.28 (−0.30, 0.86)	0.34
Other	−0.05 (−0.56, 0.45)	0.84	−0.07 (−0.57, 0.42)	0.77
Hypertension	0.27 (0.07, 0.47)	**0.01**	0.22 (−0.01, 0.45)	0.06
Diabetes Mellitus	0.22 (0.01, 0.44)	**0.04**	0.06 (−0.17, 0.28)	0.62
CKD	0.41 (0.11, 0.71)	**0.01**	0.24 (0.07, 0.56)	0.13
COPD	−0.06 (−0.37, 0.25)	0.72	−0.20 (−0.54, 0.13)	0.23
Hyperlipidemia	−0.02 (−0.22, 0.19)	0.86	−0.20 (−0.42, 0.02)	0.08
Smoking: current/former	−0.00 (−0.20, 0.20)	0.98	−0.02 (−0.22, 0.19)	0.87
BMI	−0.01 (−0.02, 0.00)	0.23	0.00 (−0.01, 0.01)	0.66

Table 3
Logistic regression models for necessity of ICU care. Adjusted model corresponds to CAC severity and is adjusted by all listed covariates (age, sex, race, hypertension, diabetes, CKD, COPD, hyperlipidemia, smoking status, and BMI).

	Unadjusted model		Adjusted model	
	Odds ratio (95 % CI)	p-value	Odds ratio (95 % CI)	p-value
CAC Severity				
None (ref)	–	–	–	–
Mild	1.89 (1.11, 3.24)	**0.02**	1.57 (0.86, 2.89)	0.14
Moderate	1.05 (0.47, 2.32)	0.91	0.84 (0.35, 2.05)	0.71
Severe	4.28 (2.01, 9.12)	**<0.001**	3.97 (1.67, 9.48)	**0.002**
Age	1.02 (1.00, 1.03)	**0.02**	1.02 (0.99, 1.04)	0.13
Sex				
Male (ref)	–	–	–	–
Female	1.08 (0.70, 1.66)	0.74	1.08 (0.65, 1.78)	0.77
Race				
NHW (ref)	–	–	–	–
NHB	1.31 (0.80, 2.17)	0.29	1.55 (0.86, 2.78)	0.14
Hispanic	1.50 (0.46, 4.95)	0.50	2.09 (0.54, 8.01)	0.28
Other	1.34 (0.47, 3.86)	0.58	1.32 (0.39, 4.50)	0.66
Hypertension	1.69 (1.06, 2.70)	**0.03**	1.30 (0.73, 2.34)	0.37
Diabetes Mellitus	1.51 (0.96, 2.38)	0.08	1.04 (0.61, 1.78)	0.89
CKD	1.93 (1.07, 3.48)	**0.03**	1.33 (0.66, 2.66)	0.43
COPD	0.88 (0.44, 1.78)	0.73	0.66 (0.29, 1.46)	0.30
Hyperlipidemia	1.29 (0.83, 2.01)	0.25	0.91 (0.53, 1.56)	0.72
Smoking: current/former	1.21 (0.78, 1.88)	0.39	1.30 (0.79, 2.15)	0.31
BMI	1.00 (0.98, 1.03)	0.91	1.02 (0.99, 1.06)	0.16

0.02) but this significance did not remain after adjustment for covariates (p = 0.23; Table A3). In the unadjusted model, mild (OR 1.89; 95 % CI 1.11–3.24; p = 0.02) and severe CAC (OR 4.28; 95 % CI 2.01–9.12; p < 0.001) were significantly associated with ICU admission compared to no CAC. After adjustment for covariates, the association between severe CAC and ICU admission remained with an OR of 3.97 (95 % CI 1.67–9.48; p = 0.002). Age (p = 0.02), hypertension (p = 0.03), and CKD (p = 0.03) were independent predictors of ICU care in the unadjusted model but were not significant after adjustment for covariates (Table 3).

3.4. ICU length of stay (LOS)

Although CAC resulted in higher rate of ICU care (Table A3), CAC was not associated with ICU length of stay. This applied to both CAC presence or absence as well as CAC severity (Table A4).

3.5. Mortality: Combined in hospital and 30 days after discharge

A total of 64 (14.0 %) patients died in the hospital or 30 days after discharge. Mortality rate was higher for those with CAC (20.2 %) compared to without (8.6 %; p < 0.001; Table 1). Mortality was significantly different across CAC groups (p = 0.001) with the no CAC group having the lowest proportion of 8.6 % and severe CAC group having the highest proportion of 27.3 % (Table A1).

Patients with CAC compared to without CAC had increased all-cause mortality in the unadjusted model (HR 2.38; 95 % CI 1.35–4.21; p = 0.003) but this significance did not remain after adjustment for covariates (Table A5). Mild and severe CAC were associated with greater mortality in the unadjusted analysis with a HR 2.43 (95 % CI 1.25–4.71; p = 0.01) for mild and HR 3.70 (95 % CI 1.61–8.51; p = 0.002) for severe CAC compared to patients with no CAC. However, in the multivariable analysis after adjustment for age and other comorbidities, CAC severity

Table 4
Cox proportional hazards models for mortality in hospital or 30 days after discharge. Adjusted model corresponds to CAC severity and is adjusted by all listed covariates (age, sex, race, hypertension, diabetes, CKD, COPD, hyperlipidemia, smoking status, and BMI).

	Unadjusted model		Adjusted model	
	Hazard ratio (95 % CI)	p-value	Hazard ratio (95 % CI)	p-value
CAC severity				
None (ref)	–	–	–	–
Mild	2.43 (1.25, 4.71)	**0.003**	1.24 (0.60, 2.57)	0.56
Moderate	2.11 (0.88, 5.04)	0.10	0.87 (0.32, 2.34)	0.78
Severe	3.70 (1.61, 8.51)	**0.002**	1.60 (0.62, 4.13)	0.33
Age	1.06 (1.03, 1.08)	**<0.001**	1.06 (1.03, 1.09)	**<0.001**
Sex				
Male (ref)	–	–	–	–
Female	0.69 (0.40, 1.18)	0.18	0.61 (0.32, 1.14)	0.12
Race				
NHW (ref)	–	–	–	
NHB	0.63 (0.30, 1.30)	0.21	0.99 (0.44, 2.20)	0.98
Hispanic	1.16 (0.28, 4.80)	0.84	2.23 (0.50, 10.01)	0.29
Other	1.33 (0.41, 4.30)	0.64	0.94 (0.22, 4.09)	0.93
Hypertension	1.43 (0.80, 2.54)	0.23	1.00 (0.49, 2.07)	0.99
Diabetes Mellitus	1.27 (0.73, 2.23)	0.40	1.06 (0.55, 2.04)	0.85
CKD	1.86 (0.96, 3.61)	0.07	1.30 (0.61, 2.77)	0.50
COPD	1.02 (0.44, 2.38)	0.97	0.85 (0.35, 2.10)	0.73
Hyperlipidemia	1.19 (0.69, 2.05)	0.53	0.68 (0.36, 1.30)	0.25
Smoking: current/former	1.37 (0.79, 2.37)	0.27	1.01 (0.55, 1.85)	0.98
BMI	0.96 (0.92, 0.99)	**0.03**	1.01 (0.97, 1.06)	0.49

Table 5
Logistic regression models for mechanical ventilation. Adjusted model corresponds to CAC severity and is adjusted by all listed covariates (age, sex, race, hypertension, diabetes, CKD, COPD, hyperlipidemia, smoking status, and BMI).

	Unadjusted model		Adjusted model	
	Odds ratio(95 % CI)	p-value	Odds ratio (95 % CI)	p-value
CAC Severity				
None (ref)	–	–	–	–
Mild	2.31 (1.19, 4.49)	**0.01**	1.76 (0.84, 3.70)	0.13
Moderate	1.44 (0.55, 3.77)	0.46	0.83 (0.28, 2.45)	0.74
Severe	4.39 (1.85, 10.39)	**0.001**	3.08 (1.13, 8.42)	**0.03**
Age	1.03 (1.01, 1.05)	**0.01**	1.03 (1.00, 1.05)	0.07
Sex				
Male (ref)	–	–	–	–
Female	0.68 (0.39, 1.18)	0.17	0.64 (0.34, 1.21)	0.17
Race				
NHW (ref)	–	–	–	–
NHB	1.05 (0.56, 1.98)	0.88	1.36 (0.65, 2.86)	0.41
Hispanic	1.13 (0.24, 5.23)	0.88	1.57 (0.27, 9.18)	0.62
Other	0.80 (0.18, 3.58)	0.77	0.44 (0.05, 3.67)	0.45
Hypertension	2.18 (1.18, 4.04)	**0.01**	1.53 (0.72, 3.25)	0.27
Diabetes Mellitus	1.71 (0.98, 2.98)	0.06	1.00 (0.52, 1.94)	>0.99
CKD	2.73 (1.41, 5.29)	**0.003**	2.13 (0.98, 4.63)	0.06
COPD	0.84 (0.34, 2.07)	0.71	0.54 (0.19, 1.52)	0.24
Hyperlipidemia	1.44 (0.83, 2.48)	0.19	0.94 (0.48, 1.82)	0.85
Smoking: current/former	1.38 (0.79, 2.40)	0.25	1.34 (0.72, 2.49)	0.36
BMI	1.01 (0.83, 2.48)	0.54	1.03(1.00, 1.07)	0.08

was not associated with combined in-hospital and 30-day mortality, with a HR 1.24 (95 % CI 0.60–2.57) for mild, HR 0.87 (95 % CI 0.32–2.34) for moderate, and HR 1.60 (95 % CI 0.62–4.13) for severe CAC compared to patients with no CAC. Age was an independent predictor of mortality in both the unadjusted and adjusted models ($p < 0.001$). BMI was an independent predictor of mortality in the unadjusted model ($p = 0.03$) but was not significant after adjustment (Table 4).

3.6. Mechanical ventilation

A total of 58 (12.7 %) patients required mechanical ventilation during admission for COVID-19. Mechanical ventilation requirement was higher for those with CAC (16.9 %) compared to without (9.0 %; $p = 0.01$; Table 1). Mechanical ventilation was significantly different across CAC groups ($p = 0.002$) with the no CAC group comprising the lowest proportion (9.0 %) and severe CAC group comprising the highest proportion (30.3 %) of patients requiring mechanical ventilation (Table A1).

Patients with CAC compared to without CAC had increased rate of mechanical ventilation in the unadjusted model (OR 2.05; 95 % CI 1.17–3.61; $p = 0.001$) but this significance did not remain after adjustment for covariates (Table A6). Mild and severe CAC were associated with higher rates of mechanical ventilation in the unadjusted analysis with OR 2.31 (95 % CI 1.19–4.49; $p = 0.01$) for mild and OR 4.39 (95 % CI 1.85–10.39; $p = 0.001$) for severe CAC compared to patients with no CAC. In the multivariable analysis after adjustment for age and other comorbidities, only severe CAC remained associated with higher rate of mechanical ventilation with OR 3.08 (95 % CI 1.13–8.42; $p = 0.03$). Age ($p = 0.01$), hypertension ($p = 0.01$), and CKD ($p = 0.003$) were independent predictors of mechanical ventilation in the unadjusted model, but none were significant predictors after adjustment (Table 5).

4. Discussion

CAC screening has been widely accepted and used as a method to identify seemingly asymptomatic people with high-risk of adverse cardiovascular events to ensure the primary prevention of CVD (such as primary prevention statin prescription and optimization of other risk factors) in the outpatient setting. The novelty of our study is the use of incidental CAC noted on non-gated chest CT to predict short-term outcomes in patients without a prior history of CAD who are hospitalized with acute COVID-19 infection.

The main findings of our study were the positive associations between CAC and hospital length of stay, ICU care, mechanical ventilation, and in-hospital or 30-day mortality. Some strengths include the large sample size of patients ($n = 457$) without prior history of coronary artery disease and a roughly even distribution of those with and without CAC. Compared to other investigations which are limited by a predominantly male cohort, our study had an even distribution of males and females [11]. Our results suggest that CAC is a significant marker of poor outcomes in hospitalized COVID-19 patients. Even after adjustment for several important covariates, compared to no CAC, severe CAC was found to be an especially strong predictor of hospital LOS, ICU requirement, and mechanical ventilation.

Current research investigating the relationship between CAC and adverse outcomes in COVID-19 are limited by small sample sizes and study period as many of the analyses were conducted on data from early in the pandemic when treatments for COVID-19 were not well-defined and testing for COVID-19 was not readily available [14–20]. In particular, some early-pandemic studies found a significant association between CAC and mortality, but it is possible that the limited COVID-19 treatments and protocols at that time may have contributed to worse outcomes and higher mortality rates [14,15]. Our study addressed these limitations by analyzing patient data over a longer period of one year and starting a few months after the onset of the pandemic.

One study of hospitalized COVID-19 patients from March 13 to April 30, 2020 showed an association between CAC and 6-month mortality in unadjusted analysis [14]. When the authors adjusted for covariates (age, sex, diabetes, HLD, HTN, obesity, and cancer) the only significant association that remained was between heavy CAC and mortality. Our unadjusted analysis showed similar associations between CAC and mortality. Importantly, we found that severe CAC was the strongest single predictor of in-hospital or 30-day mortality with HR 3.70. This was greater than all other variables, including age (HR 1.06). Although our data did not show a significant association between severe CAC and mortality in our adjusted analysis, this could be because we only had 33 subjects with severe CAC. Our study may have been underpowered to assess this relationship. The largest related study in the literature to date is of 2067 patients admitted to 22 different hospitals in China between

January and April 2020. In their multivariable Cox regression model, those with higher CAC were at increased risk of in-hospital mortality (HR 1.73; 95 % CI 1.010–2.971) and adverse clinical outcomes (combined death, ICU admission, and mechanical ventilation) [18]. This was a well-powered study showing significant association between CAC and in-hospital mortality. Therefore, it is possible that even with a large sample of 457 patients, our study was underpowered for the mortality outcome.

Although our study spanned a one-year period, very few currently published investigations have encompassed more than three months. Of those, one study of hospitalized patients from February to September 2020 found similar results in that CAC was associated with mortality and mechanical ventilation, particularly those with severe calcification [21]. Another, though small, study of 53 patients admitted to a hospital in Japan from March to August 2020 demonstrated that CAC score over 180 may be a marker of COVID-19 severity as it was associated with worsening oxygenation and requirement for more CT images of the chest. As opposed to our findings, hospital length of stay was not significantly greater for those with higher CAC score, though this was likely due to the small sample size [22].

Our results highlight the importance of reporting incidental cardiovascular findings, specifically CAC, on CT chest imaging for patients with COVID-19. Recognition of CAC on CT scans can potentially be suggestive of a prolonged clinical course and place patients at higher risk for adverse outcomes. If severe CAC is noted on chest CT, it is more likely that these patients may need ICU admission or even mechanical ventilation. Our study suggests that these patients should be prepared for longer hospital LOS and need for escalation of care. Specifically, patients with severe CAC compared to those without CAC had 3.97 times odds of ICU admission and 3.08 times odds of mechanical ventilation. CAC can be useful for risk assessment and potentially triaging to higher levels of care during initial evaluation of patients hospitalized with COVID-19.

One limitation of our study is only patients with CT chest scans done during hospital admission were included, but not all patients who were hospitalized for COVID-19 had a CT chest done during admission. This may have weakened associations with adverse outcomes, as we may have selected a sicker population. There may have also been variability in assessment of CAC on CT scans as an individual radiologist's assessment from the CT scan report was used. This may have been what led to seeing significant associations for mild and severe CAC in relation to the study outcomes but limited significant associations for the moderate CAC group. It is subjectively easier to distinguish between mild and severe than between mild and moderate or moderate and severe CAC. Although the lack of blinded radiographic interpretation and clear standardized CT interpretation criteria are weaknesses of this study, the CAC versus no CAC analyses make up for the lack of protocolization in grading CAC severity. Additionally, the patients in this study were not vaccinated for COVID-19 as widespread vaccination was not available prior to the study end date. Therefore, we cannot generalize these results to vaccinated individuals.

While our study utilized a qualitative measure of CAC, there are also quantitative methods to assess CAC on non-gated CT studies. One approach is applying the standard Agatston scoring system which is usually used as the gold standard for quantifying CAC on gated scans [8]. Studies have shown high degree of correlation between Agatston CAC scores for non-gated versus gated scans [8,23]. Another approach is an ordinal scoring system that applies an integer value to correlate with the total burden of CAC, and this has been shown to strongly correlate with Agatston scores [8,24]. These methods should be used more broadly across medical centers. While our study utilized a purely qualitative assessment of CAC and may not be as robust as quantitative approaches, our results would have been biased towards the null hypothesis if reporting were inconsistent across radiologists. Furthermore, there are multiple studies demonstrating that even simple visual assessment of CAC is prognostic and has good agreement with Agatston score categories [8,25,26]. Simple visual assessment of CAC on non-gated CT scans of the chest in hospitalized patients also provides independent prognostic information beyond traditional risk factors [27].

5. Conclusions

In patients without prior coronary artery disease who were hospitalized with COVID-19, qualitative assessment of CAC on CT chest scans can be used as a predictor of hospital length of stay, ICU care requirement, mechanical ventilation, and in-hospital or 30-day mortality. In general, those with CAC have longer hospital LOS, increased ICU requirement, higher rate of mechanical ventilation, and greater in-hospital or 30-day mortality. Even after adjustment for age and other comorbidities, severe CAC compared to no CAC is a strong predictor of hospital length of stay, ICU care requirement, and mechanical ventilation. Patients with severe CAC, and without clinical history of CAD, represent a high-risk population for morbidity and mortality when hospitalized with COVID-19. This highlights importance of visual assessment of CAC on imaging to gauge risk for adverse outcomes in patients hospitalized with COVID-19.

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Ethical statement

The authors attest that they have presented an accurate account of the work performed and an objective discussion of its significance.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2023.100288.

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