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ORIGINAL ARTICLE

Coronary Artery Calcification on Chest Computed Tomography as a Predictor of Cardiovascular Adverse Events in Patients With COVID-19

— A Multicenter Retrospective Study in Japan —

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Background: Coronary artery calcification (CAC) detected through chest computed tomography (CT) strongly predicts cardiovascular events in asymptomatic individuals undergoing primary prevention. Few studies with limited sample sizes have investigated the predictive value of CAC for cardiovascular complications in COVID-19. This study examined the impact of CAC on cardiovascular complications using a large-scale COVID-19 database.

Methods and Results: This multicenter retrospective cohort study used data from the Japan COVID-19 Task Force database. After exclusion based on missing information, 1,109 patients with COVID-19 were included. The Agatston score was used to evaluate CAC, dividing the population into 3 groups based on calcification degree (no, moderate, and severe CAC). The primary outcome was cardiovascular complications; the secondary outcome was critical outcomes. The severe CAC group had a higher rate of cardiovascular complications than the other groups. Multivariable analysis, considering COVID-19 severity factors, identified severe CAC as independently associated with cardiovascular complications but not with critical outcomes. Subgroup analysis revealed that, in patients without hypertension, diabetes, cardiovascular disease, or chronic kidney disease, severe CAC was significantly correlated with cardiovascular complications, whereas this association was not observed in patients with these underlying conditions.

Conclusions: Patients with COVID-19 and severe CAC had increased cardiovascular complications, and identifying cardiovascular and pulmonary findings on chest CT is essential. Measuring CAC via non-electrocardiogram-gated CT helps predict patient risk.

Key Words: Coronary artery calcification (CAC); COVID-19

Since December 2019, COVID-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread rapidly around the world.[1] Advances in therapeutic agents[2] and vaccines[3] against COVID-19 have reduced mortality; however, mutations in virus strains[4] and recurring epidemics[5] continue to contribute to many cases of infections worldwide. The severity of COVID-19 varies widely, making identifying patients with severe disease and establishing severity markers important for appropriately allocating medical resources as a counter-

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measure against future pandemics.

COVID-19 causes severe pneumonia and various cardiovascular complications, such as heart failure, myocardial infarction, and venous thromboembolism. Cytokine storms resulting from the immune response to COVID-19 infection and COVID-19 itself can induce myocardial injury, arrhythmia, acute coronary syndrome, and venous thromboembolism. Early identification of patients at risk of cardiovascular complications is clinically useful because these complications lead to poor outcomes.[6] A previous study reported that having cardiovascular disease (CVD) is a risk for a poor prognosis in patients with COVID-19.[7] CVD is often asymptomatic, and coronary artery calcification (CAC), quantified via electrocardiogram (ECG)-gated computed tomography (CT) examinations without using intravenous contrast material, is the most robust predictor of CVD events in the asymptomatic population undergoing primary prevention, particularly in those with an intermediate risk.[8] CAC has been associated with future cardiovascular complications in patients with chronic obstructive pulmonary disease (COPD),[9] as well as in the general population without known CVD.[10]

Chest CT is widely used in the management of COVID-19 because it is an important tool in accurately diagnosing pneumonia, determining the severity of pneumonia,[11] and evaluating extrapulmonary organs.[12] Although the association between CAC on chest CT and death has been examined,[13,14] the results have been inconsistent. One study reported that heavy CAC was independently associated with 6-month mortality in hospitalized patients with severe COVID-19 pneumonia,[13] but another study reported that the CAC score did not provide additional value over robust clinical variables in predicting in-hospital mortality.[14] These studies had small sample sizes and involved single-center settings with a single epidemic wave, which may have led to the inconsistencies.

We hypothesized that CAC can be a useful biomarker for predicting cardiovascular complications in patients with COVID-19. Therefore, the aim of the present study was to investigate the effect of CAC on cardiovascular complications in patients with COVID-19.

Methods

Study Design and Settings

Data were collected from the Japan COVID-19 Task Force database between February 2020 and October 2022.[2] The Task Force compiled clinical information on patients aged ≥18 years and diagnosed with COVID-19 through polymerase chain reaction or antigen test from 4 institutions in Japan (Keio University Hospital, Juntendo University Hospital, Saitama Medical Center, and Saitama City Hospital). Of the 1,410 patients identified, 301 were excluded for reasons such as unavailability for baseline chest CT (n=217), contrast-enhanced CT scans, lung field striations (n=58), or inability to evaluate CAC because of pacemaker or stent placement (n=26). Thus, 1,109 patients were ultimately included in the analysis (**Supplementary Figure 1**). The Ethics Committee of Keio University School of Medicine approved this study (ID: 20200061), and written or oral informed consent was obtained from all patients. All aspects of the study conformed to the principles of the Declaration of Helsinki adopted by the World Medical Association General Assembly, Fortaleza, Brazil on October 2013.

Clinical Data

Patient data obtained from the electronic case record form included age, sex, body mass index (BMI), comorbidities, clinical symptoms and signs, laboratory and radiographic findings, and complications after hospitalization. All laboratory tests and radiographies were performed within 48 h of the initial visit or admission based on the clinical care needs of the patients. The primary outcome was the percentage of patients with cardiovascular complications, defined as the occurrence of heart failure, myocardial damage/infarction, thromboembolism (including pulmonary embolism), or stroke after hospitalization.[15] The definition of myocardial damage varied considering different clinicians. The secondary outcome was the percentage of patients with critical outcomes, defined as the need for oxygen supplementation via high-flow oxygen therapy, non-invasive mechanical ventilation (IMV) and IMV, and extracorporeal membrane oxygenation or death.[12] The outcome follow-up period was the period of hospitalization.

CT Image Acquisition

All CT images were obtained after full inspiration. Images of the entire lung with a slice thickness of 1–5 mm were reconstructed using standard kernels. The SOMATOM series (Siemens Healthineers), Aquilion series (Canon Medical Systems), Revolution series (GE Healthcare), Discovery series (GE Healthcare), and BrightSpeed (GE Healthcare) CT scanners were used.

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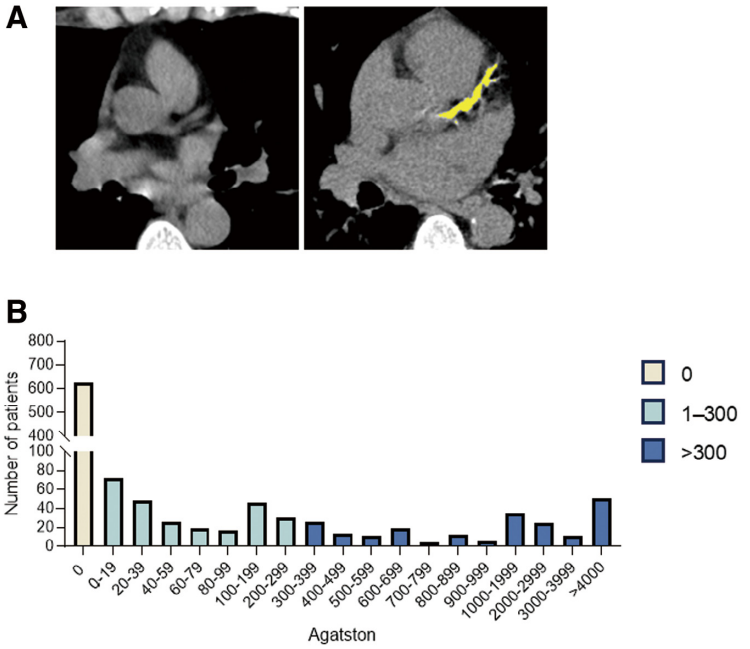

Figure 1. (**A**) Representative computed tomography (CT) images used to measure coronary artery calcification (CAC) in patients with COVID-19. The Agatston score was calculated to evaluate CAC. Areas of coronary calcium with CT density ≥130 Hounsfield units and 1 mm^2 along the coronary artery were measured on each axial slice (yellow), multiplied by a weighting factor defined based on their maximum CT density, totaled, and standardized to minimize the effect of varying slice thickness. Images were acquired using SYNAPSE VINCENT (FUJIFILM Medical Co., Ltd, Tokyo, Japan). (**B**) Patient distribution according to Agatston score.

CT Analysis of Extrapulmonary Features

CAC was quantitatively evaluated using ImageJ (Fiji) software[16] for the manual masking of target regions and custom-made Python scripts for the automatic calculation of areas. The Agatston score was calculated to assess CAC severity: areas of coronary artery calcium with a CT density ≥130 Hounsfield Units (HU) and ≥1 mm^2 along the coronary artery were measured in each axial slice (**Figure 1A**), multiplied by a weighting factor defined based on maximum CT density, summed, and standardized to minimize the effect of variation in slice thickness.[17] Throughout our study, Agatston score was measured independently by pulmonologists with 18, 10, 9, and 8 years of experience who were blinded to all clinical information in the central organization. CAC severity was categorized according to the Agatston score as follows: 0 CAC=no CAC, very low risk; 1–100=mild CAC, mildly increased risk; 101–300=moderate CAC, moderately increased risk; and >300=moderate-to-severely increased risk.[18] However, we defined Agatston scores of 1–100 and 101–300 as "moderate CAC" to compare the impact of severe CAC with that of no CAC. Therefore, we divided patients into 3 categories: no CAC (Agatston score 0), moderate CAC (Agatston score 1–300), and severe CAC (Agatston score >300).

Artificial Intelligence (AI)-Based CT Analysis of Lung Lesions

Pneumonia and total lung segmentation was performed using SYNAPSE VINCENT software (FUJIFILM, Tokyo, Japan), developed to quantify abnormal CT patterns in idiopathic pulmonary fibrosis. We measured the volume of abnormal CT patterns as pneumonia shadows in patients with COVID-19. The percentage of lung lesions was defined as volume divided by total lung volume.[11]

Statistical Analysis

Baseline variables were summarized as frequencies for categorical data and as mean±SD values for continuous variables. Data were compared among the 3 CAC groups (Agatston score 0, 1–300, and >300) using the Chi-squared test and one-way analysis of variance. The Bonferroni test was used as a post hoc test. We performed multivariable logistic regression analysis to investigate the association between each group and primary or secondary outcomes. Specifically, these models were adjusted for patient characteristics reported as predictors of COVID-19, including age, sex, BMI, pneumonia area >16%,[11] and comorbidities (hypertension [HTN], diabetes, COPD, CVD, and chronic kidney disease [CKD]).[11,19] Subgroup analyses were performed in univariate analysis, divided by the presence or absence of atherosclerotic disease. We present odds ratios (ORs) and adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Statistical significance was set at 2-sided $P<0.05$. All data were analyzed using IBM SPSS® Statistics version 27.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline Characteristics of Study Participants

Figure 1B shows the distribution of CAC in this study; the median Agatston score was 0.0 (interquartile range [IQR] 0.0–119.1). There were 630 (56.8%), 265 (23.9%), and 214 (19.3%) participants in the 0, 1–300, and >300 Agatston score groups, respectively. The baseline characteristics in each of the 3 groups are presented in the **Table**. Patients with severe CAC (Agatston score >300) were significantly older, had a higher smoking history, and had significantly more comorbidities, such as diabetes, CVD, malignancy, COPD, hyperuricemia, and CKD than the other 2 groups. Furthermore, the severe CAC group had a higher frequency of prescriptions for angiotensin-covering enzyme inhibitors or angiotensin II receptor blockers than the other 2 groups. More men than women had severe CAC. The **Supplementary Table** presents a comparison of subjective symptoms and

Table. Clinical Characteristics and Comorbidities of Patients With No, Moderate, and Severe Coronary Artery Calcification

	All patients (n=1,109)	Agatston score			P value
		0 (n=630)	1–300 (n=265)	>300 (n=214)	
Clinical characteristics					
Age (years)	56 [45–68]	50 [39–58]	62.5 [52–72]	72 [60–79]	<0.001[A]
Male sex	770 (69.4)	414 (65.7)	179 (67.5)	177 (82.7)	<0.001[B]
BMI (kg/m^2)	24.3 [21.7–27.1]	24.3 [21.9–27.5]	24.5 [21.7–27.2]	23.9 [21.4–26.2]	0.263[A]
Smoking status[C]					<0.001[B]
Current smoker	141 (12.7)	87 (13.8)	31 (11.7)	23 (10.7)	
Past smoker	369 (23.3)	173 (27.5)	96 (36.2)	98 (46.3)	
Never smoker	585 (64)	359 (57.0)	137 (51.7)	89 (43)	
Slice thickness					<0.001[B]
Thin (≤2 mm)	781 (70.4)	412 (65.4)	189 (71.3)	180 (84.1)	
Thick (5 mm)	326 (29.4)	216 (34.3)	76 (28.7)	34 (15.9)	
Comorbidities					
Hypertension	348 (31.3)	121 (19.2)	105 (39.7)	122 (57.0)	<0.001[B]
Diabetes	212 (19.1)	71 (11.3)	53 (20.0)	88 (41.1)	<0.001[B]
Cardiovascular disease	109 (9.8)	18 (2.9)	25 (9.4)	66 (30.8)	<0.001[B]
Malignancy	110 (9.9)	41 (6.5)	32 (12.0)	37 (17.3)	<0.001[B]
COPD	31 (2.8)	8 (1.3)	11 (4.2)	12 (5.6)	0.001[B]
Asthma	84 (7.6)	57 (9.0)	22 (8.3)	5 (2.3)	0.005[B]
Hyperuricemia	124 (11.2)	53 (8.4)	35 (13.2)	36 (16.8)	0.002[B]
Chronic liver disorder	33 (3.0)	20 (3.2)	4 (1.5)	9 (4.2)	0.190[B]
CKD	92 (8.3)	24 (3.8)	23 (8.7)	45 (21.0)	<0.001[B]
CKD grade[D]					0.110[B]
Grade 1	4 (0.36)	3 (0.48)	1 (0.38)	0 (0)	
Grade 2	33 (3.0)	9 (1.4)	10 (3.8)	14 (6.5)	
Grade 3	55 (5.0)	12 (1.9)	12 (4.5)	31 (14.5)	
Medications					
ACEi/ARB	225 (20.3)	70 (11.4)	72 (27.1)	83 (38.8)	<0.001[B]

Unless indicated otherwise, data are given as the median [interquartile range] or n (%). [A]One-way analysis of variance. [B]Chi-squared test. [C]Patients with unknown smoking status excluded. [D]Chronic kidney disease (CKD) grades were defined as follows: Grade 1, estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m^2; Grade 2, 30 mL/min/1.73 m^2≤eGFR<60 mL/min/1.73 m^2; Grade 3, eGFR <30 mL/min/1.73 m^2. ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

laboratory findings among the 3 groups. Patients with CAC had a lower frequency of upper respiratory tract symptoms, higher neutrophil counts, and higher levels of C-reactive protein, lactate dehydrogenase, creatinine, and serum troponin T and B-type natriuretic peptide than patients without CAC (**Supplementary Figure 2**).

Association of CAC With Cardiovascular Complications

The group with Agatston scores >300 had a higher rate of cardiovascular complications (9.9%) than the groups with Agatston scores of 1–300 (4.2%) and 0 (2.1%) groups (**Figure 2A**). In multivariable analysis, an Agatston score >300 was independently associated with cardiovascular complications after accounting for known COVID-19 severity factors, namely age, sex, BMI, underlying disease, and pneumonia severity (aOR 2.91; 95% CI 1.17–7.22; **Figure 2B**). Independent of the degree of pneumonia assessed by AI, severe CAC was associated with the development of cardiovascular complications. Individual cardiovascular complications, including myocardial damage, heart failure, and thrombotic events, were more prevalent in the group with Agatston scores >300 (**Figure 3**).

Association of CAC With Critical Outcome

Figure 4A shows a comparison of critical outcome rates between the CAC groups. The group with Agatston scores >300 had a higher rate of cardiovascular complications (12.6%) than the groups with Agatston scores 1–300 (7.5%) and 0 (7%) groups. In multivariable analysis, an Agatston score >300 was not independently associated with critical outcomes, considering known COVID-19 severity factors (aOR 1.08; 95% CI 0.53–2.19; **Figure 4B**). Conversely, pneumonia lesions analyzed using AI and diabetes were independently associated with critical outcomes, regardless of these factors, with aORs of 11.55 (95% CI 6.27–21.28) and 2.11 (95% CI 1.18–3.78), respectively (**Figure 4B**). **Figure 5** shows a comparison of individual cardiovascular complications among CAC groups, revealing no significant differences in nasal high-flow or non-invasive positive pressure ventilation or IMV ratios among the groups, but higher mortality in the group with Agatston scores >300 (P<0.001).

Subgroup Analysis of Associations Between CAC, Cardiovascular Complications, and Critical Outcomes With/Without Arteriosclerotic Disease

We performed subgroup analyses according to the presence/absence of arteriosclerotic diseases (HTN, diabetes, CVD, and CKD) to identify the specific patient population in whom CAC is a useful biomarker. Agatston scores >300

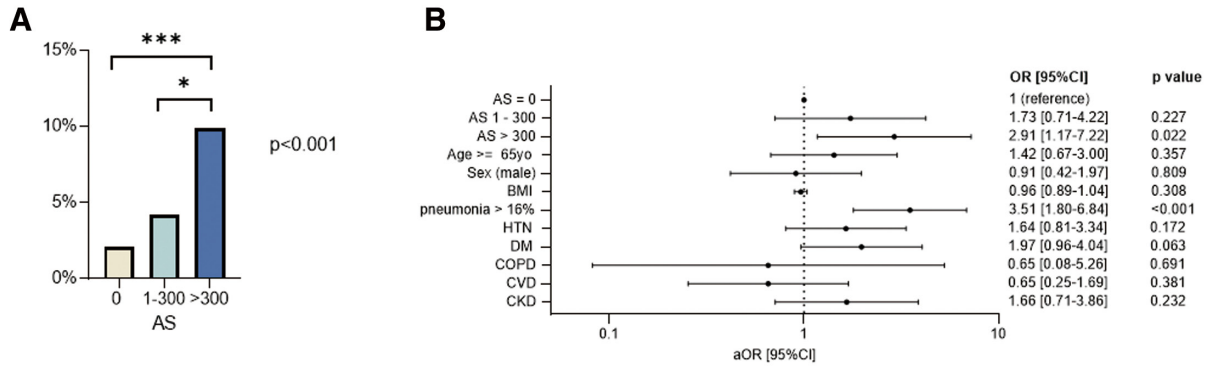

Figure 2. Association between coronary artery calcification (CAC) and the primary outcome (cardiovascular events). (**A**) Cardiovascular events in the 3 groups stratified by Agatston score (AS). *P<0.05, ***P<0.001. (**B**) Forest plot of multivariable analysis. aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes; HTN, hypertension; OR, odds ratio.

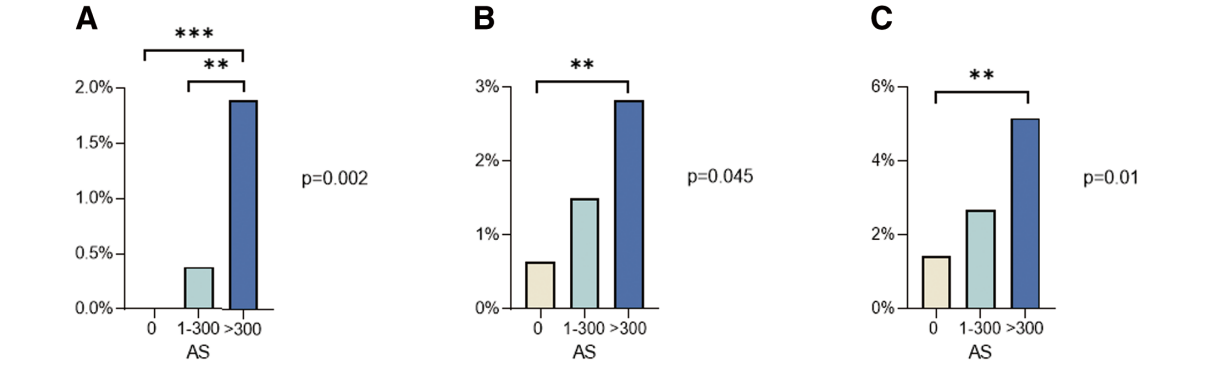

Figure 3. Incidence of each component comprising cardiovascular events in this study: (**A**) myocardial damage/infarction, (**B**) heart failure, and (**C**) thromboembolism, including pulmonary embolism or stroke. Data were compared among 3 groups stratified by Agatston score (AS; 0, 1–300, and >300) using the Chi-squared test and t-test. The Bonferroni test was used as a post hoc test. ****P<0.001, ***P=0.001, **P<0.05.

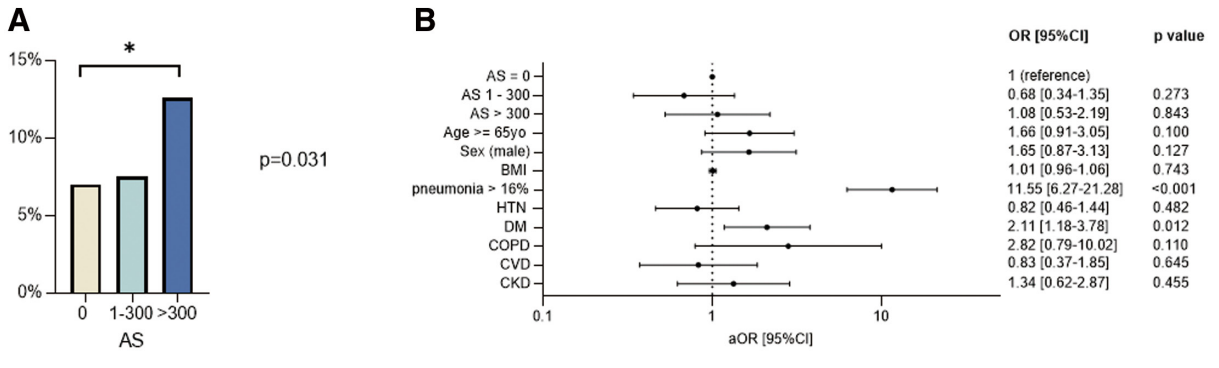

Figure 4. Association between coronary artery calcification (CAC) and the secondary outcome (critical outcome). (**A**) Critical outcomes in the 3 groups stratified by Agatston score (AS). *P<0.05, ***P<0.001. (**B**) Forest plot of multivariable analysis. aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes; HTN, hypertension; OR, odds ratio.

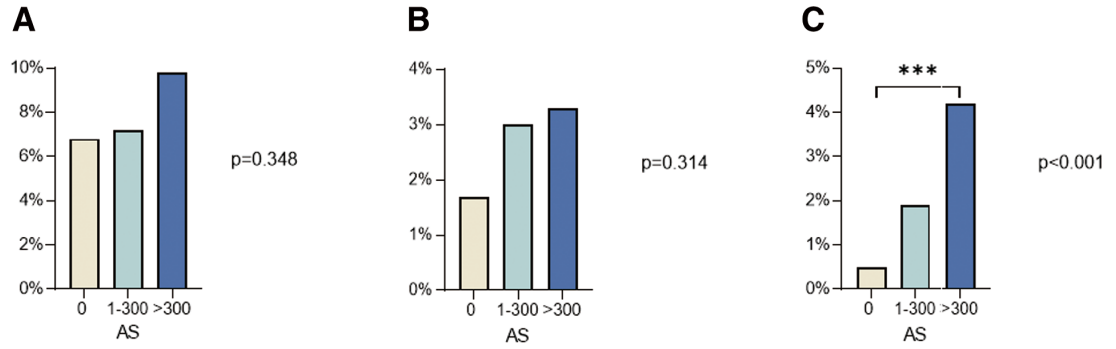

Figure 5. Incidence of each of the components of critical outcome: (**A**) nasal high flow or non-invasive positive pressure ventilation (NHF/NPPV), (**B**) invasive mechanical ventilation (IMV), and (**C**) death. Data were compared among 3 groups stratified by Agatston score (AS; 0, 1–300, and >300) using the Chi-squared test and t-test. The Bonferroni test was used as a post hoc test. ****P<0.001, ***P=0.001, **P<0.05.

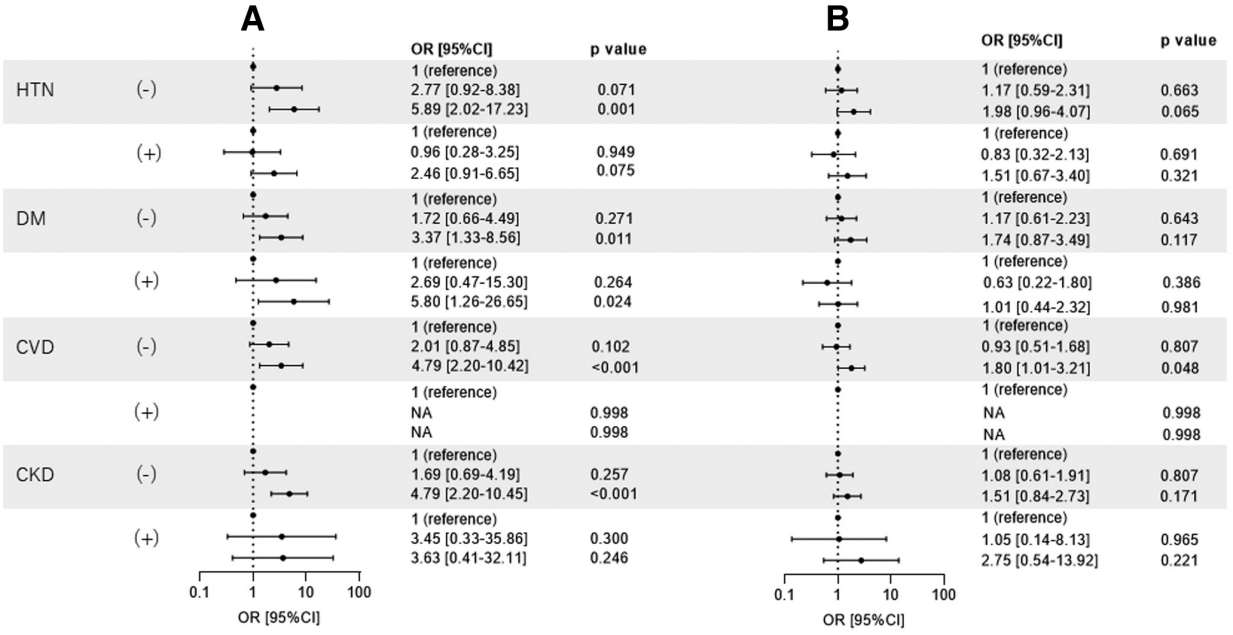

Figure 6. Univariate subanalysis with and without underlying diseases for the (**A**) primary outcome (cardiovascular events) and (**B**) secondary outcome (critical outcome). Univariate odds ratios (ORs) and P values for Agatston scores 0, 1–300, and >300 are shown in order from the top row. CI, confidence interval; CKD, chronic kidney disease; CVD, cardiovascular disease; DM, diabetes; HTN, hypertension.

were significantly associated with cardiovascular complications in patients without HTN (aOR 5.89; 95% CI 2.02–17.23), diabetes (aOR 3.37; 95% CI 1.33–8.56), CVD (aOR 4.79; 95% CI 2.20–10.42), or CKD (aOR 4.79; 95% CI 2.20–10.45), but not in patients with these underlying diseases (**Figure 6A**). Conversely, severe CAC was only associated with critical outcomes in patients without CVD (OR 1.80; 95% CI 1.01–3.21; **Figure 6B**).

Discussion

To our knowledge, this is the largest study investigating associations between CAC, quantified using the Agatston score, and cardiovascular complications in patients with COVID-19. Our multicenter analysis of large-scale patient data showed that increased CAC and cardiovascular complications were independently associated with pre-existing morbidities, and these associations were particularly strong in patients with no risk factors, such as HTN,

diabetes, or previous CVD. These results are clinically relevant in 2 aspects. First, CAC measurement is a useful biomarker that can be analyzed through routine clinical CT without additional radiation exposure or cost. Cardiovascular complications have poor outcomes in patients with COVID-19;[6] thus, identifying patients at high risk of cardiovascular complications through CAC measurement may improve the outcomes of patients with COVID-19. Second, although the presence of an underlying disease may predict cardiovascular complications, CAC measurements can be used to identify at-risk patients, because identifying patients based solely on underlying diseases is rather challenging.

COVID-19 has direct and indirect cardiac effects, resulting in cardiac complications such as acute myocardial damage, myocarditis, heart failure, and thrombosis.[6] In the present study, cardiovascular complications occurred in 4.1% of hospitalized patients, and severe CAC was associated with myocardial damage, heart failure, and thrombotic events. Only 2 studies with small sample sizes have examined the association between CAC and cardiovascular complications in patients with COVID-19.[20,21] Planek et al.[20] examined cardiovascular complications as a secondary outcome and did not perform multivariable analysis; however, they discovered that the presence of a qualitative CAC was associated with cardiovascular complications.[20] Furthermore, Luchian et al.[21] reported that the absence of CAC had a high negative predictive value for cardiovascular complications in patients hospitalized with COVID-19, even in the presence of cardiac risk factors. Our study is the first to examine the association between quantitative CAC and cardiovascular complications and perform a multivariate analysis. In our study, the association was independent of multivariate analysis and was particularly important in patients without cardiac risk factors. This result is consistent with findings in the general population, where the presence of CAC was a risk factor for cardiovascular complications in patients without cardiovascular risk factors.[22] Furthermore, in the present study, patients with severe CAC had elevated B-type natriuretic peptide and troponin T levels on admission. This result is consistent with the finding of an association between CAC and cardiovascular complications.

In our study, the association between CAC and cardiac complications was independent of the extent of pneumonia, determined using AI-based analysis. As reported previously,[11] AI-based analysis of pneumonia was useful in predicting critical outcomes; however, in the present study, CAC could predict cardiovascular complications independently of the pneumonia lesion. This suggests that evaluating CAC and pneumonia lesions may be useful in predicting high-risk patients with COVID-19. CAC is associated with arterial[10,23] and venous thrombosis, according to previous studies in the general population.[24] Although we were unable to distinguish between arterial and venous thrombosis, the association between CAC and a composite outcome, including thrombosis, is consistent with the findings of previous studies. In the general population, CAC evaluation is recommended for asymptomatic individuals aged 40–75 years with a moderate risk of atherosclerosis. Treatment with statins, aspirin, and angiotensin-converting enzyme inhibitors is recommended[25] to prevent CVD. In a retrospective study, Zhang et al.[26] reported that the in-hospital use of statins was associated with a reduced mortality risk among individuals with COVID-19. Although the efficacy of these drugs is not definite, they may be effective.[19] Evaluating CAC using CT in future studies may help identify patients who would benefit from such medical therapy.

In this study, patients with severe CAC had higher rates of critical outcomes, but multivariate analysis showed no significant differences among the CAC groups. One possible explanation may be that the difference in mortality was observed only between patients with and without CAC, with no difference in the proportion of IMV, consistent with the results of a recent meta-analysis of COVID-19 in which the association between CAC and death was more pronounced than that between CAC and IMV requirements.[23] Moreover, the association between CAC and composite outcomes in previous studies remains debatable.[20,27] Another possible reason is the duration of the study; COVID-19 has a different clinical course based on variations in viral strains and therapeutic agents.[4,5] Because this study was conducted over a long period, including relatively late cases, the number of critical outcome events may be small, resulting in non-significant differences.

The extent of CAC reflects the lifetime accumulation of the risk of atherosclerosis.[28] In the present study, patients with severe CAC were older, were more likely to be smokers, and had more comorbidities such as diabetes and HTN than those with no CAC and moderate CAC. These factors contribute to poor COVID-19 outcomes.[11,19] Differences in the degree of coronary plaque formation[29] and calcification[29,30] have been reported because of ethnic differences in these risk factors. Japanese and East Asian populations have lower cardiovascular mortality[29] and less CAC than Western populations.[30] Therefore, examining the importance of CAC in patients with COVID-19 in Japan is important. CAC severity in the present study was milder than in a previous COVID-19 study conducted in a Western country.[30] The only study on CAC and COVID-19 outcomes in Japan was a small-scale study, and it reported that a CAC score of ≥180 was associated with exacerbation of oxygenation on chest CT images during hospitalization.[31] Our study confirmed that more severe CAC, rather than mild to moderate CAC, is associated with worse outcomes in a larger cohort. In previous studies, mild<moderate <severe CAC has been associated with poor outcomes in a stepwise manner in both patients with COVID-19[12,13] and the general population.[32] In our study, only severe CAC, and not mild to moderate CAC, was associated with poor outcomes in Japanese patients with COVID-19. Our subanalysis predicted cardiovascular complications in patients without atherosclerotic disease, suggesting that these populations may include patients with undiagnosed atherosclerotic disease.[19]

Previous studies reported that slice thickness affects CAC scoring.[33] In many studies the slice thicknesses are unified,[17] with only a few not having unified slice thicknesses.[34] It should be noted that the slice thickness in the present study was not unified. In this study, we found a significant association between an Agatston score >300 and outcomes only in patients who underwent thin-slice CT, but not significant in patients who underwent 5-mm slice CT (data was not shown). Therefore, there is a need for care when generalizing our findings to patients with different slice thicknesses and other imaging conditions.

This study has some limitations. First, our study did not evaluate the long-term survival of patients. The mortality rate at 6 months after admission increased with the severity

of CAC.[13] The association between long-term cardiac complications and CAC should be examined in future research. Second, we did not examine CAC using ECG-gated CT. Traditionally, ECG-gated non-contrast CT has been used for assessing CAC.[8] However, measuring CAC using non-ECG-gated CT is a feasible option for the general population,[8] as well as in patients with COVID-19,[22,24,29] consistent with the usefulness of CT in predicting poor outcomes, as observed in our study. Third, data on regular medications used were limited. In particular, antihypertensive, antihyperglycemic, and cardiovascular drugs, as well as statins, can affect cardiovascular complications. Future studies using larger datasets are required to explore the correlation between CAC severity and cardiovascular complications after adjusting for the use of prescribed drugs. Finally, the results of the subgroup analysis of the association between CAC and outcomes with/without arteriosclerotic disease may be an underestimate because of an insufficient number of patients in each group.

In conclusion, patients with COVID-19 and severe CAC had a high rate of cardiovascular complications. Moreover, recognizing cardiovascular and pulmonary findings on chest CT in COVID-19 patients is important. CAC measurement using non-ECG-gated CT may be useful in COVID-19 practice, helping clinicians predict patient risk.

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Disclosures

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

Author Contributions

The authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

IRB Information

The Ethics Committee of Keio University School of Medicine approved this study (ID: 20200061), and written or oral informed consent was obtained from all patients.

Data Availability

The deidentified participant data will be shared on a request basis. Please contact the corresponding author (S.C.) directly to request data sharing. The entire dataset used will be available, including the study protocol. Data will be shared after approval from the IRB at Keio University School of Medicine and will be available until March 31, 2030. The data will be shared with anyone wishing to access it. All analyses on the data will be approved and data will be shared as Excel file via email.

References

1. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; **382:** 1708–1720.
2. Tanaka H, Chubachi S, Namkoong H, Sato Y, Asakura T, Lee H, et al. Propensity-score matched analysis of the effectiveness of baricitinib in patients with coronavirus disease 2019 (COVID-19) using nationwide real-world data: An observational matched cohort study from the Japan COVID-19 Task Force. *Open Forum Infect Dis* 2023; **10:** ofad311.
3. Tanaka H, Chubachi S, Asakura T, Namkoong H, Azekawa S, Otake S, et al. Characteristics and clinical effectiveness of COVID-19 vaccination in hospitalized patients in Omicron-dominated epidemic wave: A nationwide study in Japan. *Int J Infect Dis* 2023; **132:** 84–88.
4. Akkız H. The biological functions and clinical significance of SARS-CoV-2 variants of corcern. *Front Med (Lausanne)* 2022; **9:** 849217.
5. Lee H, Chubachi S, Namkoong H, Asakura T, Tanaka H, Otake S, et al. Characteristics of hospitalized patients with COVID-19 during the first to fifth waves of infection: A report from the Japan COVID-19 Task Force. *BMC Infect Dis* 2022; **22:** 935.
6. Zhao YH, Zhao L, Yang XC, Wang P. Cardiovascular complications of SARS-CoV-2 infection (COVID-19): A systematic review and meta-analysis. *Rev Cardiovasc Med* 2021; **22:** 159–165.
7. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol* 2020; **109:** 531–538.
8. Hecht HS, Cronin P, Blaha MJ, Budoff MJ, Kazerooni EA, Narula J, et al. 2016 SCCT/STR guidelines for coronary artery calcium scoring of noncontrast noncardiac chest CT scans: A report of the Society of Cardiovascular Computed Tomography and Society of Thoracic Radiology. *J Thorac Imaging* 2017; **32:** W54–W66.
9. Bhatt SP, Kazerooni EA, Newell JD, Hokanson JE, Budoff MJ, Dass CA, et al. Visual estimate of coronary artery calcium predicts cardiovascular disease in COPD. *Chest* 2018; **154:** 579–587.
10. Shao L, Yan AT, Lebovic G, Wong HH, Kirpalani A, Deva DP. Prognostic value of visually detected coronary artery calcification on unenhanced non-gated thoracic computed tomography for prediction of non-fatal myocardial infarction and all-cause mortality. *J Cardiovasc Comput Tomogr* 2017; **11:** 196–202.
11. Tanaka H, Maetani T, Chubachi S, Tanabe N, Shiraishi Y, Asakura T, et al. Clinical utilization of artificial intelligence-based COVID-19 pneumonia quantification using chest computed tomography: A multicenter retrospective cohort study in Japan. *Respir Res* 2023; **24:** 241.
12. Fukushima T, Maetani T, Chubachi S, Tanabe N, Asakura T, Namkoong H, et al. Epicardial adipose tissue measured from analysis of adipose tissue area using chest CT imaging is the best potential predictor of COVID-19 severity. *Metabolism* 2024; **150:** 155715.
13. Mousseaux E, Fayol A, Danchin N, Soulat G, Charpentier E, Livrozet M, et al. Association between coronary artery calcifications and 6-month mortality in hospitalized patients with COVID-19. *Diagn Interv Imaging* 2021; **102:** 717–725.
14. Fazzari F, Cozzi O, Maurina M, Donghi V, Indolfi E, Curzi M, et al. In-hospital prognostic role of coronary atherosclerotic burden in COVID-19 patients. *J Cardiovasc Med (Hagerstown)* 2021; **22:** 818–827.
15. Doumouras AG, Wong JA, Paterson JM, Lee Y, Sivapathasundaram B, Tarride JE, et al. Bariatric surgery and cardiovascular outcomes in patients with obesity and cardiovascular disease: A population-based retrospective cohort study. *Circulation* 2021; **143:** 1468–1480.
16. Schindelin J, Arganda-Carreras I, Frise E, Kaynig V, Longair M, Pietzsch T, et al. Fiji: An open-source platform for biological-image analysis. *Nat Methods* 2012; **9:** 676–682.
17. Agatston AS, Janowits WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; **15:** 827–832.
18. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008; **358:** 1336–1345.
19. Sakurai K, Chubachi S, Asakura T, Namkoong H, Tanaka H, Azekawa S, et al. Prognostic significance of hypertension history and blood pressure on admission in Japanese patients with

coronavirus disease 2019: Integrative analysis from the Japan COVID-19 Task Force. *Hypertens Res* 2024; **47:** 639–648.
20. Planek MI, Ruge M, Du Fay de Lavallaz JM, Kyung SB, Gomez JM, Suboc TM, et al. Cardiovascular findings on chest computed tomography associated with COVID-19 adverse clinical outcomes. *Am Heart J Plus* 2021; **11:** 100052.
21. Luchian ML, Lochy S, Motoc A, Belsack D, Magne J, Roosens B, et al. Prognostic value of coronary artery calcium score in hospitalized COVID-19 patients. *Front Cardiovasc Med* 2021; **8:** 684528.
22. Nasir K, Rubin J, Blaha MJ, Shaw LJ, Blankstein R, Rivera JJ, et al. Interplay of coronary artery calcification and traditional risk factors for the prediction of all-cause mortality in asymptomatic individuals. *Circ Cardiovasc Imaging* 2012; **5:** 467–473.
23. Peng AW, Dudum R, Jain SS, Maron DJ, Patel BN, Khandwala N, et al. Association of coronary artery calcium detected by routine ungated CT imaging with cardiovascular outcomes. *J Am Coll Cardiol* 2023; **82:** 1192–1202.
24. Hong C, Zhu F, Du D, Pilgram TK, Sicard GA, Bae KT. Coronary artery calcification and risk factors for atherosclerosis in patients with venous thromboembolism. *Atherosclerosis* 2005; **183:** 169–174.
25. Golub IS, Termeie OG, Kristo S, Schroeder LP, Lakshmanan S, Shafter AM, et al. Major global coronary artery calcium guidelines. *JACC Cardiovasc Imaging* 2023; **16:** 98–117.
26. Zhang XJ, Qin JJ, Cheng X, Shen L, Zhao YC, Yuan Y, et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. *Cell Metab* 2020; **32:** 176–187.e4.
27. Dillinger JG, Benmessaoud FA, Pezel T, Voicu S, Sideris G, Chergui N, et al. Coronary artery calcification and complications in patients with COVID-19. *JACC Cardiovasc Imaging* 2020; **13:** 2468–2470.
28. Berman DS, Arnson Y, Rozanski A. Coronary artery calcium scanning: The Agatston score and beyond. *JACC Cardiovasc Imaging* 2016; **9:** 1417–1419.
29. Chua A, Adams D, Dey D, Blankstein R, Fairbairn T, Leipsic J, et al. Coronary artery disease in East and South Asians: Differences observed on cardiac CT. *Heart* 2022; **108:** 251–257.
30. de Ronde MW, Khoshiwal A, Planken RN, Boekholdt SM, Biemond M, Budoff MJ, et al. A pooled-analysis of age and sex based coronary artery calcium scores percentiles. *J Cardiovasc Comput Tomogr* 2020; **14:** 414–420.
31. Takeshita Y, Terada J, Fujita R, Hirasawa Y, Kinoshita T, Isaka Y, et al. Coronary artery calcium score may be a novel predictor of COVID-19 prognosis: A retrospective study. *BMJ Open Respir Res* 2021; **8:** e0000923.
32. Zimmermann GS, Fingerle AA, Müller-Leisse C, Gassert F, von Schacky CE, Ibrahim T, et al. Coronary calcium scoring assessed on native screening chest CT imaging as predictor for outcome in COVID-19: An analysis of a hospitalized German cohort. *PLoS One* 2020; **15:** e0244707.
33. Kim JY, Suh YJ, Han K, Choi BW. Reliability of coronary artery calcium severity assessment on non-electrocardiogram-gated CT: A Meta-analysis. *Korean J Radiol* 2021; **22:** 1034–1043.
34. Silva BV, Menezes MN, Plácido R, Jorge C, Rigueira J, Garcia AB, et al. Coronary artery calcium identified on non-gated chest CT scans: A wasted opportunity for preventive cardiological care. *Heart Lung Circ* 2023; **32:** 1312–1320.

Supplementary Files

Please find supplementary file(s);
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