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# Coronary artery calcium score as a prognostic factor of adverse outcomes in patients with COVID-19: a comprehensive review

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**Abstract:** *Background and aim:* **The association of known cardiovascular risk factors and poor prognosis of coronavirus disease 2019 (COVID-19) has been recently emphasized. Coronary artery calcium (CAC) score is considered to be a risk predictor of cardiovascular events. Therefore, we have conducted a review of literature on the predictive value of CAC score predictive value in COVID-19 outcome.** *Method:* **A search of literature was conducted, aiming for articles published until December 2021 on PubMed and Scopus to identify potentially eligible studies.** *Discussion:* **A total of 18 articles were reviewed for association between higher CAC score and adverse outcomes in COVID-19.** *Conclusion:* **The coronary calcium score could be considered as a new radiological marker for risk assessment in COVID-19 patients and providing additional information in fields of prognosis and possible cardiovascular complications. High CAC score is associated with higher in-hospital death and adverse clinical outcomes in patients with confirmed COVID-19, which highlights the importance of calcium load**

testing for hospitalized COVID-19 patients and calls for attention to patients with high CAC scores. (Curr Probl Cardiol 2022;00:101175.)

## Introduction

Since the first confirmed case in Wuhan, China in December 2019, the Coronavirus disease 2019 (COVID-19) has been declared as a pandemic disease; infecting millions of people around the world.[1] COVID-19 infection may manifest a wide array of symptoms, including common forms of mild and unspecific constitutional symptoms, along with more severe complications such as respiratory failure, sepsis, and acute cardiac injury. All of which may require intensive care treatments and ventilation.[2-5] Patients with pre-existing cardiovascular comorbidities are more presumably predisposed to COVID-19 infection complications.[6-9] As previous literature has noted the association of higher complication rates and mortality rates in COVID-19 patients with pre-existing hypertension, diabetes mellitus, or a past history of cardiac events.[10,11] Although several studies have investigated the correlation of COVID-19 infection and atherosclerosis-related diseases, there are limited number of studies that report quantitative data and measurements related to atherosclerotic features observed.[12,13] Coronary artery calcification (CAC) score is a reliable and quantitative predictor of cardiovascular events and mortality by utilizing various scoring systems such as Agatston score and volume score.[14-16] CAC scoring is a highly sensitive method with high negative predictive value which could be used as the solitary prognostic method for estimating risk of Cardiovascular disease.[17] However, the prognostic role of CAC score in acute systemic inflammatory diseases, such as COVID-19, has not yet been investigated. Chest CT imaging is a common work-up procedure for COVID-19 patients. This imaging modality demonstrates the extent of pulmonary dysfunction, detects COVID-19 infection in suspected patients, and may be used as screening tool for COVID- 19 in patients with severe respiratory insufficiency.[18,19] These data may lead us to an imaging biomarker in COVID-19 patients; resulting in further insight into the disease process, reduction of unnecessary work-up procedures, and estimation of required intensive care unit beds prior to patients' complications occurrence. We herein aim to evaluate short-term prognostic value of CAC in patients with COVID-19 infection, along with discussing the probable pathophysiologic mechanisms of COVID-19 adverse effects.

## Methods and Materials

A comprehensive review of literature was performed to collect currently available data on using coronary artery calcium score in COVID-19 patients as an imaging marker for adverse outcomes. In order to identify qualified studies, a comprehensive search was conducted on PubMed and Scopus, aiming the articles published from January 2020 to December 2021.The search was carried out using the following strategy: (1) Language restriction was not applied. (2) Related articles function on PubMed was used to extend the search, followed by (3) the manual search of the bibliography to find other potentially eligible studies. The search results were screened by title and abstract, and the potentially relevant articles selected for full-text evaluation. Data extraction was conducted in a double data extraction method by two independent reviewers (F.Y, E.G), followed by a precise reevaluation of included articles by 2 other members of authoring team (A.R, I.K.)

## Review of Articles

We reviewed the association between the presence and severity of CAC as an independent risk factor and adverse outcomes in COVID-19 in 18 articles. The adverse outcomes included in this review consisted of all-cause mortality, ICU requirement, and ventilation requirement. Further details of these articles are presented in Table. Among 18 articles under study, 17 articles were retrospective cohort or cross-sectional studies and 1 was letter to editor. CAC score assessment method used in the articles are 7 visual assessment (n = 7), Agatston (n = 5), volume score (n = 1), and both volume score and Agatston (n = 2). Two articles solely examined whether the calcified plaque is present or not. The association between CAC score with hypertension, dyslipidemia or smoking status was heterogeneous between the studies. *P*-value lower than 0.05 was considered statistically significant and COVID-19 was laboratory-confirmed in all patients.

### *All-Cause Mortality*

In 14 articles, higher CAC score was associated with higher all-cause mortality rate, in 1 there was no association between the two. Three articles did not state the association between all-cause mortality rate and higher CAC score.

**TABLE.** Review of literature on CAC score association with adverse outcomes in COVID-19

| Article | Sample size | Average age | Female sex (%) | CACs assessment method | CACs association with | | |
|---|---|---|---|---|---|---|---|
| | | | | | All-cause mortality | ICU requirements | Ventilation |
| Mousseaux et al, 2021[28] | 169 | 65.6 ± 15.8 | 30.1 | V-CACs | Associated | Not Associated | Associated (both invasive and noninvasive ventilation) |
| Planek et al, 202[29] | 245 | NM | 42 | CAC presence or not | Associated with 60 days mortality, Not associated with In-hospital Mortality | Not Associated | Not Associated |
| Giannini et al, 2021[30] | 1093 | 68 | 32.1 | Agatston and volume assessment | Associated | NM | Not associated with Noninvasive ventilation, Associated with invasive ventilation |
| Dillinger et al, 2020[12] | 209 | 62 | 28 | CAC presence or not | Not Associated | NM | Associated with Noninvasive ventilation, Not associated with Invasive ventilation |
| Slipczuk et al, 2021[31] | 493 | NM | 50.5 | V-CACs | Associated | NM | NM |
| Luo et al, 2021[32] | 2067 | 50 ± 15.6 | 46.9 | V-CACs | Associated | Associated | Associated with invasive ventilation |
| Gupta et al, 2021[33] | 180 | 68 | 45.6 | V-CACs | Associated | NM | Not Associated |

*(continued on next page)*

**TABLE.** (*continued*)

| Article | Sample size | Average age | Female sex (%) | CACs assessment method | CACs association with | | |
|---|---|---|---|---|---|---|---|
| | | | | | All-cause mortality | ICU requirements | Ventilation |
| Fervers et al, 2021[34] | 89 | 58.1 ± 15.9 | 44.9 | Agatston | Associated* | Associated* | Associated* |
| Takeshita et al, 2021[35] | 53 | 66.7 | 50.9 | Agatston | NM | NM | NM |
| Cereda et al, 2021[36] | 1565 | 67.9 ± 13 | 33.4 | volume assessment | Associated | NM | Associated with invasive ventilation |
| Zimmermann et al, 2020[37] | 109 | 61.8 ± 17.5 | 30.1 | Agatston | Associated | Associated | NM |
| Scoccia et al, 2021[38] | 1625 | 69 | 32.8 | Agatston | Associated | NM | NM |
| Fazzari et al, 2021[39] | 282 | 64 ± 13 | 29.8 | Agatston | Associated | Not Associated | Not Associated (both noninvasive and invasive ventilation) |
| Luchian et al, 2021[40] | 280 | 63.2 ± 16.7 | 42.5 | V-CACs | NM | Not Associated | NM |
| Colombi et al, 2020[41] | 248 | 68 | 29.8 | V-CACs | Associated | NM | NM |
| Cereda et al, 2021[42] | 1683 | 67 ± 14 | 32.8 | Agatston and volume assessment | Associated | NM | NM |
| Nair et al, 2021[43] | 67 | NM | 4.5 | V-CACS | NM | NM | NM |
| Cosyns et al, 2020[44] | 280 | NM | NM | NM | Associated | NM | NM |

CACs, Coronary Artery Calcium score; NM, Not mentioned; V-CACS, visual assessment of CACs.
*CAC score association with mortality, ICU requirements and ventilation was not evaluated separately.

## ICU

In 3 articles higher CAC score was associated with higher ICU requirement; while in 4 studies, there were no associations. 11 articles did not evaluate to the association between ICU requirement and higher CAC score.

## Ventilation

In 5 articles higher CAC score was associated with higher ventilation (invasive or noninvasive) rate. However, 4 articles have found no associations, and 9 articles did not report any data about the association between ventilation rate and higher CAC score.

Furthermore, 2 articles did not mention any associations between CAC score and mortality, ICU admission, or requirement of ventilation. However, higher CAC score had a positive correlation with deterioration of oxygenation and COVID-19 severity in these studies.

# Discussion

The Inflammatory response toward COVID-19 infection precipitates major course of the disease, including multiorgan involvement.[20] Early diagnosis and treatment of systemic or local inflammatory reaction is the key to eluding severe complications. Cardiovascular involvement is one of the most common complications in COVID-19 patients.[21]

Vessel calcification is an atherosclerotic change in the vessel walls that occurs in multiple cardiovascular diseases. CAC illustrates the lifetime aggregate burden of all for atherosclerotic risk factors.[16] among the risk factors of atherosclerotic calcification are older age, active smoking, diabetes mellitus, dyslipidemia and arterial hypertension;[22,23] All of which are also known to be associated with poor COVID-19 outcome. Since Low-dose chest CT (LDCT) is routinely obtained from COVID-19 patients in most health centers,[18,19,24] it can also be used to evaluate the heart and coronary vessels function to some extent. Calcified atherosclerotic plaques are detected via their higher intrinsic contrast relative to the adjacent soft tissue. Three commonly used grading systems for clinical quantification of CAC are (1) Agatston score, (2) visual assessment of coronary artery calcification, and (3) volume score. The Agatston score reflects both the volume of calcification and highest attenuation of calcified atherosclerotic plaques on a CT scan. Visual assessment of coronary artery calcification is a simple scoring system for classifying coronary artery calcification into 4 levels: none, mild, moderate or heavy.[25,26] The

volume score has scanning parameters similar to the Agatston score. However, it relies on estimating the true volume of calcified plaque, instead of lesion density.[27]

Our review has some limitations. The articles we reviewed determined different endpoints for mortality, ranging from in hospital mortality to 6 months mortality. This may cause bias in qualitative analysis of the outcomes.

## Conclusion

Our findings emphasize the potentially useful assessment of CAC during chest-CT imaging of COVID-19 patients. We noted that CAC can be used as an additional risk predictor of all-cause mortality in COVID-19 patients. The major strengths of CAC score is reporting both qualitative and quantitative data, cost-efficiency, and the ability to assess both prospectively and retrospectively in the studies. However, the association between higher CAC score and higher ICU requirement and ventilation rate is not clear yet and more studies are required.

## Authors Contribution

F.Y and E.G performed the search and data extraction and full-text review. A.R and I.K. investigated the correctness of included articles and performed second investigation on full-text of articles. E.G, F.Y contributed to table preparation. F.Y and A.R performed manuscript preparation. I.K performed final revision.

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