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ASSOCIATION BETWEEN CORONARY ARTERY CALCIUM SCORE AND COVID-19 PROGNOSIS

Soleimani Sh.[1], Motamedi O.[2], Amjad G.[1], Bagheri S.M.[3], Moadab M.[1], Yazdipour N.[4], Benam M.[1]

[1] Department of Radiology, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.
[2] Assistant Professor of Radiology, Department of Radiology, School of Medicine, Hazrat-e Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran.
[3] Assistant Professor of Radiology, Department of Radiology, School of Medicine, Hasheminejad Kidney Center, Iran University of Medical Sciences, Tehran, Iran.
[4] Department of Radiology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

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Abstract

Background: Research has examined the relationships between coronary artery calcium (CAC) scores and mortality, mechanical ventilation, and intensive care unit admissions. This paper summarizes the predictive value of coronary artery calcification scoring for hospitalized COVID-19 patients in terms of mortality, mechanical ventilation, and intensive care unit admission.

Methods: The patients in this single-center retrospective analysis have COVID-19 and were hospitalized at the Firouzabadi hospital in Tehran between 2019 and 2020. coronary artery calcificationscore was estimated based on chest non-contrast CT scans on the day of admission. Based on the coronary artery calcification *score, the patients were categorized into Very Low, Mild to Moderate, and Moderate to Severe. After a univariate analysis of the critical factors, odds ratio (OR) analysis and multivariate analysis of variables that could be linked to COVID-19 advancement were carried out.*

Results: a total of 719 patients were examined. Among them, 414 patients were men. Mortality with a 17.1 % prevalence was statistically significant between CAS score levels (P < 0.001). This factor has high OR with mild to moderate and moderate to severe CAS (OR: 2.14; 95% CI: 1.71 to 3.06, and OR: 2.31; 95% CI: 1.84 to 3.57). Oxygen saturation was a significant statistic between CAS score levels (P = 0.02). This factor has a high OR with mild to moderate and moderate to severe CAS (OR: 1.09; 95% CI: 0.71 to 3.60, and OR: 2.38; 95% CI: 0.89 to 2.9). There was no statistical difference between the groups' outcomes of mechanical ventilation and admission types.

Conclusion: In this study, the coronary artery calcification scores of patients with COVID-19 were compared, while the outcomes of interest mortality, mechanical ventilation, and intensive care unitU admission were closely investigated. In light of these findings, coronary artery calcificationscoring can help in patient stratification, enabling earlier therapies for disorders to progress quickly.

Keywords: *Respiratory Tract Diseases, Coronavirus Infections, COVID-19, Coronary Artery, Calcium Score.*

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Address for Correspondence:
Shakiba Soleimani
Department of Radiology, School of Medicine, Hazrat-e Rasool General Hospital, Iran University of Medical Sciences, Tehran, Iran.
Tel.: +98-61-33750410
E-mail: neuroimaging75@gmail.com

Introduction

In December 2019, a type of pneumonia of unknown cause broke out in Wuhan, China. After a short period, this disease has spread from Wuhan to other parts of China and other countries [*Asselah T et al. 2021*]. Through gene sequence analysis, the virus responsible for this pandemic has been named SARS-CoV-2 by the International Committee on Classification of Viruses (ICTV), and this disease was named COVID-19 by the World Health Organization (WHO) [*Ludwig S, Zarbock A 2020; She J et al. 2020*]. On April 6 In, 2019, this disease was declared a pandemic by the World Health Organization. Until April 20, 2019, more than one million four hundred thousand patients have been confirmed, and more than eighty thousand deaths due to this virus have been reported [*Cucinotta D, Vanelli M 2020*]. Given the highly contagious nature of the virus and the lack of preventive/therapeutic strategies, early diagnosis of COVID-19 can play an essential role in identifying and isolating infected patients. Despite the high diagnostic accuracy of RT-PCR, it has been shown that early RT-PCR may have a limited role in ruling out COVID-19 infection due to its low sensitivity of 30-60%. Also, evidence shows that a CT scan of the chest (CT) is a more sensitive method for diagnosing COVID-19 pneumonia on the first visit, with a sensitivity of 56 to 94% [*Habibzadeh P et al. 2021; Kevadiya B et al. 2021*].

Due to the initial involvement of the respiratory system, a CT scan of the chest is recommended in suspected cases of COVID-19, both for initial evaluation and follow-up [*Awulachew E et al. 2020; Kwee T, Kwee R 2020*]. Chest radiographs have been shown to have little diagnostic value in the early stages, whereas CT findings may be present even before the onset of symptoms. A chest radiograph may show the development of acute respiratory syndrome (ARDS) in the intermediate to advanced stages of the disease. In addition, it has been proven that CT scan findings are diagnostic in several patients with a false negative RT-PCR screening test [*Gaia C et al. 2020; Yang W et al. 2020*].

The severity of several diseases, including atherosclerosis-related conditions like hypertension, diabetes, and coronary artery disease, is known to be correlated with COVID-19 [*Nishiga M et al. 2020*]. According to a number of reports, a high percentage of COVID-19 patients who are seriously ill are said to have diseases related to atherosclerosis [*Aggarwal G et al. 2020; Madjid M et al. 2020; Mehta C et al. 2020; Ikari Y et al. 2021; Scoccia A et al. 2021*]. However, only a few papers have quantified the amount of atherosclerosis to show their association with COVID-19 [*Del Brutto O et al. 2022*]. The coronary artery calcium score can quantify coronary artery calcification (CAC), a CT finding indicating atherosclerosis (CACS) [*Neves P et al. 2017*]. This study's aim was to assess the prognostic value of CACS in COVID-19 patients using changes in mortality and morbidity indices.

Materials and Methods

Study design and subjects: This cross-sectional study retrospectively examined the CT scan findings in patients with COVID-19. For this purpose, patient data were collected from Firouzabadi Hospital in Tehran province from March 2018 to May 2019, and electronic medical records were analyzed. CT images and clinical data of outpatients were collected by phone call to check comorbidity, and inpatients were collected by checking electronic file files regarding comorbidity.

Clinical assessment: To check the CT scan, high-resolution scans in all patients with 64-slice multi-detector CT scanners (Toshiba Aqualion-64, Philips Brilliance-64, General Electric Speed-64, Siemens Syndication-64, and NewsoftWiz-64) were done. Patients were scanned from the apex of the lung to the xiphoid angles in the supine position during breath holding. The desired parameters were as follows: Tube voltage 100-120 kV, tube current 110-280 mA, or one smart milliamp per second (50-300 mAs), step 1.375, FOV 350-400 mm. Images with a thickness of 1.25 mm or 2.5 mm were reconstructed using a high-frequency reconstruction algorithm, and lung coils were stored in the PACS system. Two senior radiologists independently read all images. The location, shape, number, and size of CT scan abnormalities and scores were carefully observed and recorded according to the guidelines.

In this study, patients were first divided into four groups: outpatients, hospitalized in the ward, hospitalized in intensive care unit (ICU), and deceased, and then all CT scans were reviewed, and radiological findings were recorded for each patient. Also, the prognosis of the patients in this study was examined based on symptoms, hospitalization in the intensive care unit, intubation, and death.

The score for coronary artery calcium

Every artery received a calcium score of 0, 1, 2, or 3, corresponding to absence, mild, moderate, or severe CAC. A third or less of the vessel length was considered mild CAC, one third to two third was considered moderate CAC, and more than two thirds of the vessel length was considered severe CAC. Each vessel's score was added up to create the overall score. The final classifications were 0 (undetectable), 1-3 (mild), 4-5 (moderate), and 6 for the overall score (severe) [*Luchian ML et al. 2021*].

Statistical analysis: The central index of the mean and the dispersion index of the standard deviation were used to check the data distribution. Univariate and multivariate regression analysis was used to evaluate the diagnostic potential of the studied variables. All analyzes were performed using SPSS statistical analysis software, version 25. First, the prevalence of imaging findings was estimated as the percentage of patients who showed each abnormality. The Pearson correlation coefficient test was used to check the relationship between clinical and demographic data with the incidence of each finding. Also, the Odds ratio (OR) test was used to check the incidence of severe disease in people with different radiological backgrounds. The measured data were expressed as mean and standard deviation. One-way analysis of variance was used to analyze the data. A P value of less than 0.05 was considered to be statistically significant. Finally, the power of analysis and data was checked by Sample power analysis, and if the power of 80% was reached, the study results were reported as acceptable with sufficient power.

Table 1.

Demographic and clinical information on arrival for all patients.

Variables		Number = 719
Gender, Male, N (%)		414 (57.5)
Age, years, mean ± SD		69.7 ± 4.21
Calcium score, N (%)	Very Low	388 (53.8)
	Mild to Moderate	191 (26.4)
	Moderate to Severely	139 (19.3)
Admission type, N (%)	Outpatient	364 (50.6)
	Hospitalization	355 (49.4)
	ICU	152 (21.1)
Underlying diseases/ comorbidities, N (%)	Pregnancy	4 (0.6)
	Hypertension	135 (18.8)
	COPD	26 (3.6)
	CAD	84 (11.7)
	CLD	12 (1.7)
	CKD	35 (4.9)
	Autoimmune	13 (1.8)
	Malignancy	12 (1.7)
	Smoking	33 (4.6)
	Diabetes	134 (18.6)
Clinical Signs, N (%)	Shortness of breath	232 (32.2)
	Cough	163 (22.6)
Oxygen saturation percentage, mean ± SD		87.62±10.03
Length of hospitalization (days), mean ± SD		9.05 ± 8.48
Follow-up, N (%)	Intubation	54 (7.5)
	Mortality	123 (17.1)

Results

Study Characteristics: In this study, a total of 719 patients were examined. Among them, 414 patients were men. In the studied population, there was a range of comorbidities. The most common comorbidities were high blood pressure (18.8%), diabetes (18.6%), and coronary artery disease (11.7%). Also, the reported clinical symptoms included cough, dyspnea, and secretions, with the highest prevalence of symptoms related to dyspnea (32.2%) (**Table 1**).

Admission

In this analysis, there was not a significant statistic between admission types (outpatient, hospitalization, and ICU) and CAS score levels (P > 0.05). However, hospitalization and ICU types were associated with CAS in COVID-19 patients with OR > 1 (**Table 2**).

Oxygen saturation

Oxygen saturation was a significant statistic between CAS score levels (P = 0.02). This factor has high OR with mild to moderate and moderate to severe CAS (OR: 1.09; 95% CI: 0.71 to 3.60, and OR: 2.38; 95% CI: 0.89 to 2.9) (**Table 2**).

Mortality

Mortality with a 17.1 % prevalence was statisti-

Table 2.

CAS and deterioration of some variables in COVID-19 patients.

Variables	CACS Odds ratio; 95% CI			P-Value
	Very Low	Mild to Moderate	Moderate to Severely	
Outpatient	0.21; 0.15–0.42	0.11; 0.09–0.23	0.57; 0.21–0.80	0.54
Hospitalization	0.14; 0.1–0.53	1.41; 1.01–1.50	1.3; 0.96–1.65	0.68
ICU	1.04; 0.74–1.15	1.54; 1.3–3.06	1.61; 1.49–2.95	0.9
Oxygen saturation	1.013; 0.91–1.07	1.09; 0.71–3.60	2.38; 0.89 – 2.9	0.02
Mortality	0.94; 0.69–1.12	2.14; 1.71–3.06	2.31; 1.84–3.57	< 0.001
Mechanical Ventilation	0.7; 0.63–1.4	1; 0.81–1.93	1.04; 0.93–1.64	0.39
Shortness of breath	0.89; 0.66 –0.97	1.08; 0.23 –4.06	2.78; 0.39 –5.29	0.97
Cough	0.83; 0.75–0.99	1.26; 1.12–1.37	1.42; 1.17–1.84	0.078

cally significant between CAS score levels ($P < 0.001$). This factor has high OR with mild to moderate and moderate to severe CAS (OR: 2.14; 95% CI: 1.71 to 3.06, and OR: 2.31; 95% CI: 1.84 to 3.57) (**Table 2**).

Mechanical Ventilation

Mechanical ventilation was not statistically significant between CAS score levels ($P = 0.39$). This factor has high OR with mild to moderate and moderate to severe CAS (OR: 1; 95% CI: 0.81 to 1.93, and OR: 1.04; 95% CI: 0.93 to 1.64) (**Table 2**).

Discussion

The key finding of this study is that compared to other general risk factors for admission types mechanical ventilation, patients with high COVID-19 and CAC scores may be more significantly connected with death and oxygen saturation.

There are several ways to define CAC scoring; Agatston scoring, volume scoring, mass scoring, and visualization scoring (V-CACS). Patients with elevated atherosclerosis risk can be identified and risk-stratified using the clinical application of the CAC score [*Shabestari A 2013; Yousefimoghaddam F et al. 2022*]. A non-contrast computed tomography of the chest, which may be performed during COVID-19 diagnosis, can be used to determine the CAC score. The actual used scoring and cutoffs for coronary examinations are user and institution-dependent, although standardized cutoff values for CAC have previously been evaluated [*Neves P et al. 2017*].

This analysis sought to provide a mechanism for comparing CAC scores to aggregate data, given the variation in study methodologies. Only a few research [*Gaia C et al. 2020; Yang W et al. 2020*] used V-CACS to categorize the patients as absent, mild, moderate, or severe. Agatston format scores were reported in other investigations [*Dillinger J et al. 2020; Fazzari F et al. 2021; Lee K et al. 2022; Mousseaux E et al. 2021; Pergola V et al. 2022*] .

According to one study, there were “low CAC” and “high CAC” groups [*Zimmermann G et al. 2020*]. The reviewers divided the data into low-CAC and high-CAC groups based on the supplied information. Since the authors’ opinions formed the basis of this distinction, observer bias might have affected it. Objective data on the existence or absence of CAC were examined to reduce the possibility of observer bias. The probability of three clinical outcomes—death, mechanical ventilation, and ICU admission—was evaluated using these two measures. In hospitalized COVID-19 patients, a coronary atherosclerotic disease (CAD) history has been linked to a 10% increased mortality risk [*Luo S et al. 2022*]. Similar results have been found in another research. Furthermore, COVID-19 has been linked to several cardiovascular issues [*Madjid M et al. 2020*].

Even with additional cardiac risk factors, CAC demonstrated a high negative predictive value for severe adverse cardiac events in patients hospitalized with COVID-19. According to the analysis, hospitalized COVID-19 patients had a higher mortality risk when CAC was present alone. It may be safe to assume that individuals without a known CAD history will benefit from a CAC score as a predictive indicator for hospital death [*Ferrante G et al. 2020*].

Acute respiratory distress syndrome (ARDS), a primary respiratory illness that can cause COVID-19, may necessitate mechanical ventilation in many individuals [*Luchian ML et al. 2021*]. Noncardiogenic pulmonary edema, which can cause life-threatening hypoxia due to improper oxygen exchange within the lung parenchyma, defines as ARDS. Although low tidal volume mechanical ventilation is the basis of care for critically sick patients, ARDS therapy in COVID-19 is interdisciplinary [Bai C et al. 2020]. Age, obesity, cardiovascular disease, and socioeconomic status are a few variables that can increase the likelihood of needing mechanical ventilation [*Arentz, M, et al. 2020*].

Heart failure had an odds ratio of 1.9 in a single-center cohort study of 5279 patients, making it the highest risk factor for developing severe illness and the need for intubation [*Botta, M, et al. 2021*]. Whether CAC was a potential risk factor for intubation and mechanical ventilation was the goal of this investigation. Among the studies examined, *Luo et al.* (2021) found a higher risk of mechanical ventilation with high CAC scores, but the total data did not support this conclusion. All other examined studies concluded that there was no discernible increase in the risk of mechanical ventilation associated with CAC levels. These findings imply that in hospitalized COVID-19 patients, CAC presence and severity are not standalone risk factors for mechanical ventilation.

Patients with COVID-19 who are hospitalized are more likely to develop multi-organ systemic diseases. The median time from admission to critical care services was 2.5 days after the onset of symptoms, according to a study of 138 patients who experienced critical illness [*Petrilli C.M, et al. 2020*]. Although the infection's acute pulmonary insult can be blamed for this rapid deterioration, many patients also have other non-pulmonary problems requiring ICU admission. During these admissions, acute renal injury, encephalopathy, thrombosis, and heart injury are among the most frequently discovered complications [*Botta, M, et al. 2021*]. Cardiomyopathy, arrhythmia, myocardial infarction, and cardiac arrest have all been cardiac problems [*Gabarre P et al. 2020; Wang D, et al. 2020*]. Cardiomyopathy was detected in 33 percent of critically ill COVID-19 patients in a single-center cohort [*Goyal P et al. 2020*]. This cardiomyopathy is generally assumed to be either direct viral pathogen harm to the cardiac myocytes or the hypercoagulable state from elevated inflammation leading to coronary thrombosis and ischemic heart disease [Arentz, M, et al. 2020]. However, it is still unclear how these problems contribute to serious adverse cardiovascular outcomes. In a study of 700 severely ill COVID-19 patients with arrhythmias, nine individuals experienced cardiac arrest while all were in the intensive care unit. Acute in-hospital mortality was linked to the development of cardiac arrest [*Zheng Y et al. 2020*]. Early prognosis by CAC scoring may be helpful to risk-stratify patients because of the short median time from admission to an ICU transfer and the recognized cardiovascular problems that follow. For the risk of ICU admission, there was no discernible difference between high and low CAC scores. Whether or not a CAC was discovered, there was also no discernible difference in the likelihood of ICU admission. These results suggest that the probability of ICU admission for hospitalized COVID-19 patients is multivariate but unrelated to CAC scores.

Conclusion

The collected data indicate that coronary artery calcification was linked to an almost 2-fold increase in mortality. Uncertainty exists regarding the precise mechanism via which coronary artery calcification raises mortality rates. It could be brought on by myocarditis, type 1 or 2 myocardial infarctions, or other factors such as a higher risk of cardiac arrest. It is well-recognized that coronary atherosclerosis poses a considerable risk for unfavorable outcomes in COVID-19 hospitalizations. Through the coronary artery calcification score, patients without a documented history of coronary atherosclerotic disease can be non-invasively evaluated for potential coronary atherosclerosis. In this patient population, coronary artery calcification scoring may not be correlated with the probability of mechanical breathing or intensive care unit admission. In light of these findings, coronary artery calcification scoring can help in patient stratification, enabling earlier therapies for disorders to progress quickly.

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(+37493 588697 Editor-in-Chief
Fax: (+37410) 582532
E-mail:namj.ysmu@gmail.com, ysmiu@mail.ru
URL:http//www.ysmu.am

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