European Review for Medical and Pharmacological Sciences 2023; 27: 2173-2181

Coronary calcifications as a new prognostic marker in COVID-19 patients: role of CT

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Abstract. – OBJECTIVE: COVID-19 pneumonia, caused by the virus Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), was declared a pandemic by the WHO on 11th March 2020. While Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) represents the diagnostic gold standard of infection, computed tomography (CT) has been shown to have an important role in supporting the diagnosis, quantifying the severity, and assessing the efficacy of treatment and its response. Coronary artery calcification (CAC) is a CT finding that estimates atherosclerosis and can be quantified using the coronary artery calcium score (CACS). The purpose of this study is to demonstrate the correlation between coronary artery calcification and mortality rate in COVID-19 patients.

PATIENTS AND METHODS: Three hundred seventeen (317) hospitalized patients with SARS-CoV-2 infection were ruled in this retrospective study. All patients underwent a non-ECG-gated chest CT to evaluate lung parenchymal involvement. In the same cohort, we observed the two main coronary arteries (common trunk, circumflex, anterior interventricular and right coronary heart) using a visual score, so patients were divided into four groups based on Ordinal CAC Score (OCS) levels.

RESULTS: The multivariate analysis proved that the OCS value was statistically correlated with the mortality rate (*p* < 0.001). In fact, in the group of patients with an OCS value of 0, the mortality rate was 10.1% (10/99 patients), in the group with OCS between 1 and 4 was 18.9% (21/111), in the OCS group of patients ranged from 5 to 8 was 30.4% (24/79) and in the OCS group between 9 and 12 was 46.4% (13/28).

CONCLUSIONS: We suggest that calcific atheromasia of the coronary arteries in patients with COVID-19 can be considered a prognostic marker of clinical outcome.

Key Words:
COVID-19 pneumonia, SARS-CoV-2, Computed tomography (CT), Imaging, Calcification, Coronary artery calcification (CAC), Ordinal CAC Score (OCS).

Introduction

COVID-19 pneumonia, caused by the virus SARS-CoV-2, was reported in China (Wuhan) in December 2019 and it spread rapidly in many countries until the WHO declared it a pandemic on 11th March 2020[1,2]. SARS-CoV-2 is a highly contagious infection that is transmitted through respiratory droplets. The main symptoms are dry cough, fever, fatigue, and malaise. In the advanced stages of the disease, patients may develop severe dyspnea and respiratory distress syndrome (ARDS).

Skin lesions such as erythematous rashes and urticaria are infrequent and do not correlate with disease severity[3]. A significant increase in inflammatory response may damage the heart and blood vessels with an increased risk of myocarditis and vasculitis, responsible in severe cases of cardiac arrhythmias and damage of heart tissue which may lead to myocardial infarction[4]. Although most arrhythmic events are temporary, some may be permanent. Renal involvement in SARS-CoV-2 infection is associated with an increased risk of mortality[5]. Renal involvement correlates with the severity of the symptoms of COVID-19 and is more important in patients admitted to intensive care units and in elderly patients[4]. Some inflammatory/hematologic parameters have been investigated regarding the severity of disease or predictors of short-term mortality[6].

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The challenge for the healthcare providers concerns the most appropriate clinical management of the disease[7].

It is well known that Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) represents the diagnostic gold standard, but diagnostic examinations, primarily CT, have a central role for the diagnosis. CT examinations permit the quantification of the severity of lung involvement and the assessment of treatment response, allow us to monitor the progression of the disease and to evaluate the multiorgan involvement. Using CT, we learnt to recognize the typical pulmonary presentation[8].

Typical SARS-CoV-2 pneumonia is characterized by bilateral, multilobar, peripheral and subpleural ground glass opacity, with parenchymal consolidations, and thickening of the interlobular septa with crazy paving patterns in the advanced stages of the disease[9].

CT findings are sensitive but not specific for coronavirus, in fact other pneumonia types resembling COVID-19, such as viral and *Pneumocystis jirovecii* pneumonia, cryptogenic organizing pneumonia, acute lung injury from drug toxicity, hypersensitivity and autoimmune diseases[10].

In the context of the COVID-19 pandemic, there is a need for ready-to-use resources for data acquisition, computerized tools, and artificial intelligence algorithms to speed up the search for effective and safe treatments[11]. The advantages of the software are automated measurements of wall thickness for airway analysis and lobe segmentation[12]. It has been observed that both CT visual quantitative analysis and CT computerized software-based assessment of the lung involvement by COVID-19 may be useful to evaluate the distribution and the severity of COVID-19 pneumonia[13].

Many papers[14-17] reported an association between atherosclerosis-related disorders, which include hypertension, diabetes, coronary artery disease and COVID-19 severity. An important indicator of atherosclerosis on chest CT exams is the presence of calcifications of coronary arteries. CAC (coronary artery calcification) can be quantified using the Coronary Artery Calcium Score (CACS). There are various methods for the assessment of CACS. The Agatston method is the primary approach for calculating CACS. This method uses the weighted sum of lesions with a density above 130 HU and multiplies the area of calcium by a factor related to maximum plaque attenuation. The Agatston CAC score can be interpreted and classified by adjusting values for patient age, gender, and ethnicity and calculating distribution percentiles in the general population using several population databases[18]. Other visual methods for the assessment of CACS, like the OCS (Ordinal Calcium Score), can be used for the quantification of coronary artery calcifications on ungated CT scans.

The purpose of this study is to demonstrate the correlation between coronary artery calcification and mortality rate in hospitalized COVID-19 patients.

Patients and Methods

Study Sample

In the present study, we evaluated a population of 317 patients (male 196; female 121; mean age 69,5) who tested positive for nasopharyngeal swabs for COVID-19, and who underwent a chest CT at the "Policlinico di Bari" COVID Hospital, Italy, from March 2020 to April 2021, with different SARS-CoV-2 genotypes in line with the various waves, to observe lung parenchymal involvement.

The inclusion criteria were: (a) infection of SARS-CoV-2 tested by RT-PCR assay for nasal and pharyngeal swab; (b) available chest CT; (c) patients older than 40 years, because we expected that young patients do not have significant coronary calcifications, so we reduced the age bias.

The exclusion criteria were: (a) negative RT-PCR; (b) CT identification of percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) (Figure 1).

Chest and Scanning Protocol

Non-contrast non-ECG-synchronized CT examinations were performed using the Siemens Somatom Definition DS CT scanner (Milan, It-

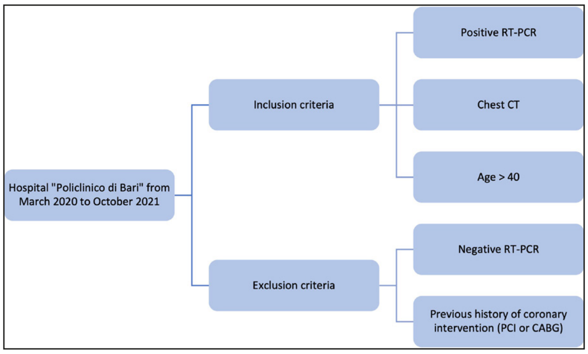

Figure 1. Inclusion and exclusion criteria.

aly) with the following acquisition parameters: slice thickness 0.75 mm, tube voltage 100 kV, 38 mAs, rotation time 0.33 s, pitch 1.1. When possible, considering patient conditions, breath-holding at full inspiration was required to acquire images. Reconstruction of images was performed with a slice thickness of 1 mm (to optimize the signal-to-noise-ratio) in mediastinal and parenchymal windows.

Imaging Assessment

Institutional PACS system (Carestream Health, Rochester, NY, USA) was used to visualize the acquired CT data. CT scans were acquired with a standard non-ECG-gated chest CT protocol.

Images were then analyzed using Multiplanar Reformatting (MPR) and displayed with two gray-scale windows, namely the lung window and mediastinal window settings, the latter to evaluate coronary artery calcifications. Visual assessments were performed independently by two radiologists (A.S.I. and N.M.); disagreements were resolved by open discussion.

Lung parenchyma was observed with a standard lung window, with a window level of -450 HU and a window width of 1400 HU.

The pulmonary findings were described according to the Fleischner Society glossary and according to current literature[19]. A semi-quantitative CT-score system, which ranged from 0 to 5 points for each lobe, reaching a maximum of 25 points for both lungs, was used to estimate the lung involvement. The percentage volume of lung lobe involvement was expressed using a score from 0 to 5: 1 point if lung lobe involvement was <5%; 2 points between 5% and 25%; 3 points between 26% and 49%; 4 points between 50% and 75%; 5 points >75%[20]. A score lower than 15 was considered a low score level, whereas a score between 15 and 25 was considered a moderate to severe score level.

For calcium quantification, CT scans were visualized using a standard mediastinal window, with a window level of -40 HU and a window width of -350 HU.

In this study, to quantify the CAC burden we adopted a visual assessment from the conventional chest CT examinations, the Ordinal Calcium Score.

Ordinal Calcium Score

Ordinal Calcium Score requires that each of the four main coronary segments were identified (left main, left anterior descending, circumflex, and right). Calcifications in all arteries were classified as absent, mild, moderate, or severe and scored by the radiologist as 0, 1, 2, or 3, respectively. Calcifications were classified as absent if no coronary artery calcification was visualized, mild when less than 33% of the length of the entire artery showed calcification, moderate between 33% and 66% of the length of the artery showed calcification, and severe when more than 66% of the artery showed calcification. Adding the score assigned to each coronary artery, each patient received a CAC score ranging from 0 to 12. Then patients were divided in four categories of CAC: 0 (undetectable), 1-4 (mild), 5-8 (moderate), 9-12 (severe) (Figure 2).

Statistical Analysis

Statistical analyses were executed using IBM SPSS Statistics Software version 26 (IBM Corp., Armonk, NY, USA). Mean, median and standard deviation (SD) were used to describe continuous variables, and the frequency with percentage was used for categorical variables.

Chi-square test was used to compare the increase in OCS value with the increase in age, mortality rate and CT Severity Score. If the p-value was <0.005, the results were considered statistically significant.

Results

Patients in the study cohort (Table I) were divided into four groups based on OCS levels: 99/317 patients (31.2%) with an OCS value of 0, 111/317 patients (35%) with an OCS between 1 and 4, 79/317 patients (25%) with an OCS between 5 and 8, and 28/317 patients (8.8%) with an OCS between 9 and 12 (Table II and Figure 3).

We observed that patients with high CAC were older (mean age in the group with OCS 0: 59 *vs.* mean age in the group with OCS 9-12: 77) (Table III and Figure 4); in fact, our analysis showed a high association between OCS groups and age groups (p-value < 0.001) (Table IV).

Patients were divided into three groups of age (40-59, 60-79, >80), and the CT Severity score was calculated for each patient in order to evaluate lung involvement. We observed that the mean CT Severity Score was comparable in these three groups (Figure 5).

As summarized in Table IV, OCS groups and CT severity scores were compared and it was ob-

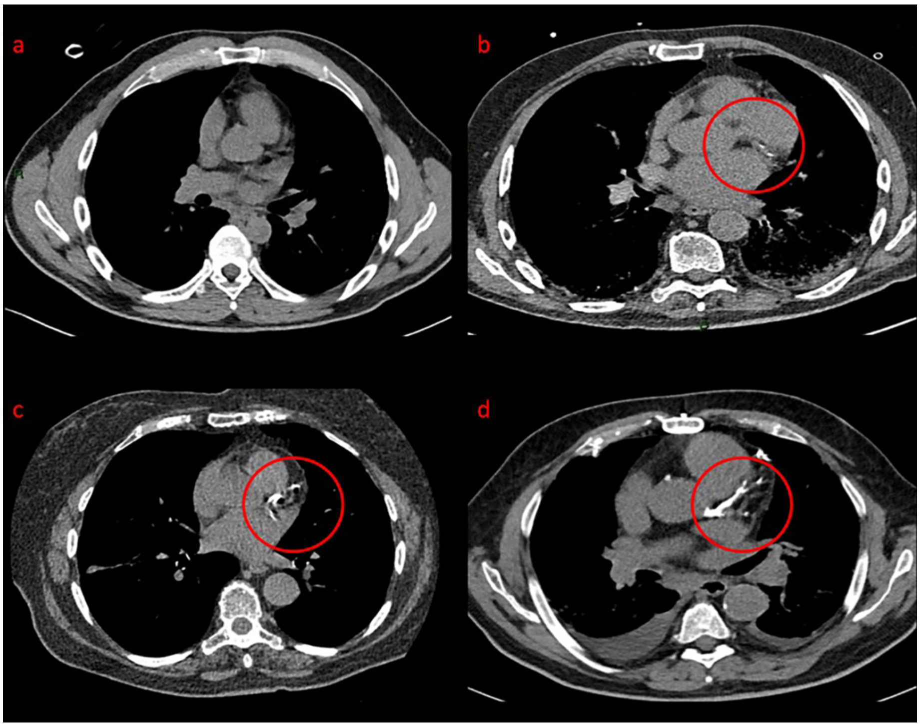

Figure 2. CAC evaluation of patients with COVID-19 **a,** Point 0 (absent): no coronary calcification is observed on chest CT image; **b,** Point 1 (mild): only isolated spot of CAC is seen within a coronary segment (in the circle); **c,** Point 2 (moderate): 66% of the artery showed calcification (in the circle); **d,** Point 3 (severe): continuous CAC are displayed within a segment (in the circle).

Table I. Population in study cohort and subdivision in groups of age, OCS and CT Severity Score.

Variables	N	%
Subjects	317	
Mean age	69.5	
Age groups (years)		
40-59	81	25.6
60-79	158	51.1
≥ 80	78	23.3
Gender		
Males	196	61.8
Females	121	38.2
OCS Groups		
0	99	31.2
1-4	111	35
5-8	79	25
9-12	28	8.8
CT Severity Score		
< 15/25	121	38.2
≥ 15/25	196	61.8
Death/population (Mortality rate)	68/317	21.5

served that there was no statistical significance, in fact pulmonary involvement was similar regardless of OCS (Figure 6) (p-value = n.s.).

The mortality rate in the cohort was 21.5% (68/317 patients), with slightly higher mortality rates in males (24/121 female and 44/196 male) (Table V).

Finally, we compared the mortality rate in the four OCS groups. In the group with the OCS value of 0 the mortality rate was 10.1% (10/99 patients), in the group with OCS between 1 and 4 was 18.9% (21/111), in the group with OCS between 5 to 8 was 30.4% (24/79) and in the group with OCS between 9 and 12 was 46.4% (13/28) (Figure 7).

There was a strong correlation between mortality rate and OCS severity (p-value <0.001) (Table IV).

Table II. This table demonstrates the number of males and females divided according to the severity of OCS score.

	OCS groups				
	0 (undetectable)	1-4 (mild)	5-8 (moderate)	9-12 (severe)	Total
Male	57	74	46	19	196
Female	42	37	33	9	121
Total	99	111	79	28	317

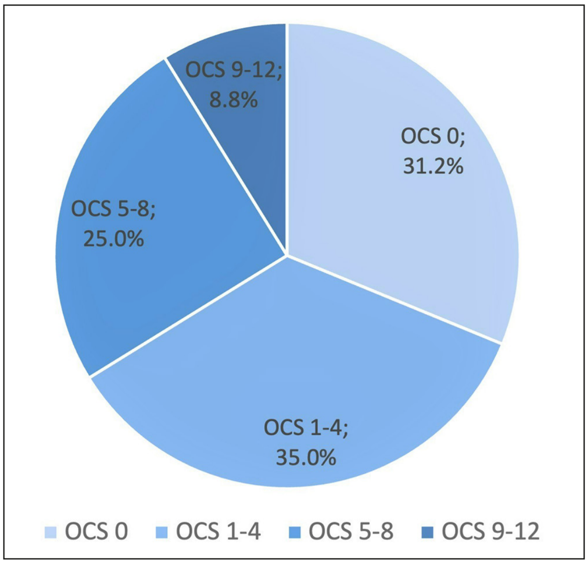

Figure 3. This figure shows the population divided into four groups of OCS.

Discussion

Chest CT is used to identify COVID-19 pneumonia[21,22]; moreover, it is helpful for easily detecting and quantifying CAC[23], i.e., an indicator of coronary atherosclerosis. Other studies[24,25] demonstrated a significant correlation between the visual assessment in non-ECG-gated chest CT examinations and the Agatston score categories.

In our study, COVID-19 patients were divided into four groups of OCS according to the degree of CAC severity. We adopted visual assessment from the conventional chest CT examinations to quantify CAC burden, and we observed that the groups with low OCS (OCS 0 and OCS between 1-4) were more extensive than groups with higher OCS (OCS between 5-8 and OCS between 9-12); in particular, as shown in Figure 3, 66,2%

Table III. Population demographics: population mean age and standard deviation (SD) for each severity group.

OCS	Mean age	Standard deviation	Median age
0 (undetectable)	58.9	10.3	58
1-4 (mild)	71.5	12.3	70
5-8 (moderate)	77.1	11.8	77
9-12 (severe)	77.0	11.8	77
Total	69.5	13.7	69

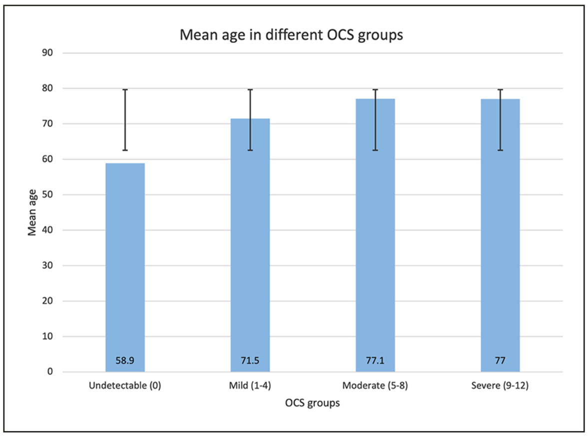

Figure 4. Mean age and standard deviation for each severity group.

Table IV. Chi-square results (*p*-value) of correlation between the increase of OCS value and analyzed variables.

	Increasing age	Mortality rate	CT Severity Score
OCS value	< 0.001	< 0.001	0.243

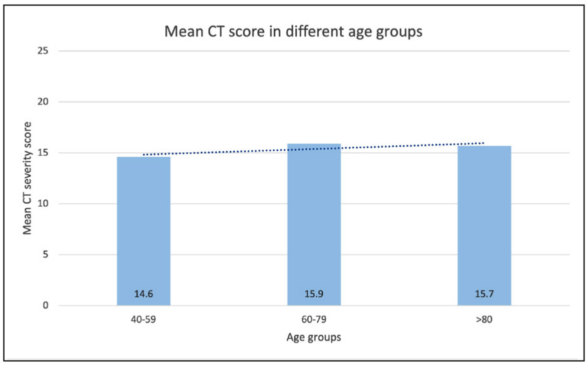

Figure 5. Values of mean CT Severity Score in three different age groups.

Table V. Evaluation of mortality rate in our population, divided in males and females.

	Females	Males
Death number	24	44
Patients	121	196
Mortality rate	19.8%	22.5%

of the patients had low OCS *vs*. 33,8% that had higher OCS. As expected, patients with severe OCS were older than patients in the other groups (Table III).

The sample has been standardized by eliminating the age bias; for this reason, in our cohort were included patients older than 40 years.

From dividing patients into three different age groups (40-59, 60-79, >80), we obtained that there were no differences in the CT Severity Score values; this reveals that the increase of age was not related to a higher CT Severity Score (Figure 5). Moreover, we calculated CT Severity Score in each OCS groups and we found that there was no correlation between the presence of coronary artery calcification and a severe lung parenchymal involvement, in fact the mean CT Severity Score of each group was approximately comparable, as shown in Figure 6.

The data we focused on was mortality, in fact from the comparison of the mortality rate and the increase of the OCS value it has been observed that the mortality increases as the severity of OCS increases, regardless of gender (mortality rate: 22.5% male *vs*. 19.8% female) (Table V) and lung parenchymal involvement (mean CT severity score was comparable in all groups) (Figure 6). In particular, the mortality rate in the group of patients without calcification (OCS 0) was 10% and in the group of patients with severe calcification (OCS 9-12) increased to 46%, hence COVID patients with higher OCS had a higher risk of death (Figure 7).

This underlines that the CAC score could be considered as a new marker for risk assessment in COVID-19 patients and as a prognostic factor for adverse outcomes, as emerged from our study and current literature[26-30].

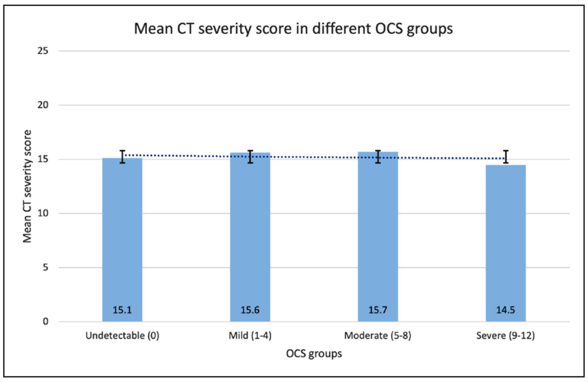

Figure 6. Mean CT Severity Score and Standard deviation (SD) in each group: no statistical differences were observed in the four groups, in fact pulmonary involvement was similar regardless of OCS.

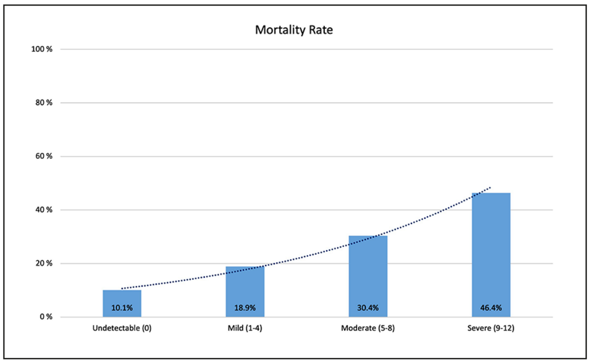

Figure 7. Comparisons between the mortality rate in the four different OCS groups.

Limitations

This study has some limitations. First, some data were of poor quality for the breathing-related artifacts and because of the presence of ICU devices. Second, we observed only CT without injection of iodinated contrast material, so it was impossible to evaluate other pathologies such as embolism. Furthermore, we considered mortality rate regardless of anamnestic data and patient management. Finally, we evaluate only the correlation between CAC and mortality, without considering the association with other risk factors. Further studies are needed to illustrate the role of these factors.

Conclusions

This study shows that high CAC can be considered a risk factor strongly associated with death in patients with COVID-19. This defines the importance of using the coronary artery calcium score for COVID-19 patients and highlights the importance of focusing on CAC severity to better assess the risk stratification and correct management of patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This research received no external funding.

Authors' Contribution

Conceptualization, Nicola Maggialetti and Arnaldo Scardapane (A.S); methodology, Paola Lazzari, Andrea Torrente and Ilaria Villanova; validation, Amato Antonio Stabile Ianora, Angela Sardaro, Nicola Maria Lucarelli, Vincenza Granata; formal analysis, Paolo Marvulli and Andrea Torrente; investigation, Ilaria Villanova; data curation, Roberto Maresca; writing—original draft preparation, Paola Lazzari and Andrea Torrente; writing—review and editing, Nicola Maggialetti and Roberto Maresca; visualization, Paolo Marvulli; supervision, Arnaldo Scardapane. All authors have read and agreed to the published version of the manuscript.

Ethics Approval

The present clinical study was conducted at the University of Bari (Italy), in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki and the additional requirements of Italian law. Furthermore, the University of Bari, Italy, classified the study as being exempt from ethical review as it carries only negligible risk and involves the use of existing data that contain only non-identifiable information about human beings. The patients signed a written informed consent form.

Informed Consent

Informed consent was obtained from the subjects involved in the study. Written informed consent was obtained from the patients to publish this paper. All 317 patients provided routine informed consent for all medical acts and for the publication of radiological images in this article.

Data Availability Statement

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