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REVIEW ARTICLE

Systematic review and meta-analysis on coronary calcifications in COVID-19

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Abstract

Chest CT is valuable to detect alternative diagnoses/complications of COVID-19, while its role for prognostication requires further investigation. Non-pulmonary radiological findings such as cardiovascular calcifications could increase the predictivity of clinical outcomes of COVID-19 patients beyond pulmonary involvement. Several observational studies have reported mixed results on the role of coronary calcifications in COVID-19 patients as a predictor of hospitalization, ventilatory support, and mortality. The purpose of the study is to systematically review the available evidence on the predictive role of cardiovascular calcifications in SARS-CoV2 disease. The meta-analysis confirms the prognostic significance of coronary calcifications on hospital mortality, and coronary calcifications (CAC ≠ 0) were associated with an OR for mortality of 2.19 (95% CI 1.36–3.52). CAC was neutral on respiratory outcomes, but it was associated with an increased trend of cardiovascular events. Coronary calcium appears as a promising biomarker imaging even in short-term outcomes (MACEs, hospital mortality) in a non-cardiovascular disease such as Sars-CoV2 infection. Further large studies are needed to confirm promising results of this imaging biomarker in non-cardiovascular disease.

Keywords COVID-19 · Coronary calcifications · Cardiovascular calcifications · CAC · CACS · CAC-DRS · Biomarker imaging

Abbreviations

CAD	Coronary artery disease
CAC	Coronary artery calcifications
CACS	Coronary artery calcium scoring
CAC-DRS	Coronary Artery Calcium Data and Reporting System
COVID-19	Coronavirus disease 2019
MACE	Major adverse cardiac events
OR	Odds ratio
RAAS	Renin-angiotensin-aldosterone system

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Introduction

Chest CT has a potential role in the diagnosis, detection of complications, and prognostication of coronavirus disease 2019 (COVID-19) [1].

In the early pandemic stages, chest CT was a rapid and reliable triage tool to refer patients requiring hospitalization to the COVID + or COVID − hospital units, when response times for virological tests were too long, to decrease congestion in the emergency departments.

The diagnostic role has lost clinical importance due to the growing technological evolution and availability of molecular and antigenic tests.

Meanwhile, the role of CT imaging in assessing prognosis, triaging patients, and identifying acute pulmonary complications associated with SARS-CoV-2 infection is still relevant.

CT imaging also may be used to stratify the severity of lung involvement, to evaluate the need for hospitalization, and to predict clinical outcomes [2].

There are several non-pulmonary radiological findings on thoracic imaging that are predictors of outcomes, such as pleuro-pericardial effusion, enlargement of the pulmonary artery, and thromboembolic manifestations [3].

Among these, the role of cardiovascular calcifications (coronary, valvular aortic, and thoracic aortic) emerged as a promising biomarker imaging to stratify the clinical evolution of the disease and predict clinical outcomes.

Considering the impact of cardiovascular disease on COVID-19 outcomes, the integration of chest CT imaging with biomarker imaging such as calcium score could play an ever-larger role in the assessment of COVID-19-related issues [4–6].

Cardiovascular calcifications and coronary artery calcium (CAC) indirectly reveal plaque burden and are a biomarker of atherosclerosis.

Both SCCT and Society of Thoracic Radiology jointly recommend the routine reporting of CAC score in routine non-contrast CT chest irrespective of indication for early detection of CAD and future research potential [7].

Cardiovascular and especially coronary calcifications can be measured using non-gated non-contrast chest CT. Various methods have been used for the evaluation of CAC (Agatston, calcium volume, semi-quantitative vessel score, and visual score).

Although the method of CAC scoring is different between quantitative and the visual method, final categories, risk prediction, and management are similar.

CAC is typically quantified using the Agatston score, a sum of the attenuation (in Hounsfield units) and area of all CAC lesions in the coronary arteries. The Coronary Artery Calcium Data and Reporting System (CAC-DRS) classifies patients based on either visual or quantitative assessment of coronary artery calcification. These scoring systems provide a simple method to indicate the overall severity of disease to the referring physician.

Cardiovascular calcifications are an emerging biomarker in the cardiovascular field. Coronary artery calcium is a highly specific marker of subclinical atherosclerosis that can be quantified using non-contrast computed tomography [8].

A CACS of 0 can down-stratify a patient's risk, whereas a CAC > 100 identifies increased cardiovascular risk.

Higher CAC burden is strongly associated with incident sudden cardiac death beyond traditional risk factors, particularly among primary prevention patients with low-intermediate risk [8].

The calcium score is proving to be an interesting marker also in the oncology field and in the outcomes of respiratory diseases, where cardiovascular health influences survival [9].

Recent cohort studies have shown a CACS 100–300 as a sign of increased cancer risk. CAC scoring as part of low-dose CT lung cancer screening can be used as an independent predictor of all-cause mortality and cardiovascular events [10].

Purpose of the study

The study was aimed to systematically analyze the available data on cardiovascular calcifications in patients with Sars-CoV2 infection.

Methods

A systematic review was carried out according to PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and was registered on Prospero (ID 307,133).

Literature search and selection criteria

An online search was conducted in PubMed, Embase, Google Scholar, and Scopus databases on 25th May 2021 to detect the studies to include in the meta-analysis.

As search terms, we included "cardiovascular calcifications AND COVID-19," "coronary artery calcifications AND COVID-19," "coronary artery calcium AND COVID-19," and related terms.

We also looked at the reference list of the included papers to detect additional eligible studies. Studies were included if they analyzed the relationship between cardiovascular calcifications (intended as coronary artery, aortic valve and/or thoracic aorta calcifications) and different types of outcomes (e.g., intubation and/or mortality, etc.). No limitation to language, sample size, or publication date was applied. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used for data selection. The eligibility of the retrieved items was independently assessed by two authors (LA and AC) and there was no disagreement. In the identification and screening phase, 22 reports were identified. Due to a lack of adequate CAC reporting and duplicates, only 11 studies were eventually included.

Data extraction

The data extraction was performed by two reviewers (LA and AC); the extracted data included (1) sample characteristics (age, female sex, arterial hypertension, and diabetes mellitus); (2) presence of coronary artery calcification (CAC) (defined as > 1 mm2 or density > 130 Hounsfield units), values of coronary artery calcium score (CACS), and prevalence of visual coronary artery calcium score and coronary artery calcium data and reporting system (CACS-DRS) categories; and (3) prevalence of COVID-19 outcomes (hospital survival, intubation, major adverse cardiac events—including acute coronary syndrome, pulmonary embolism, and stroke—and mortality).

The CAC scoring (Agatston, volume or visual) between the different studies was reassessed independently by two reviewers.

Risk of bias and quality of evidence assessment

We used the GRADE criteria to assess the quality of evidence for each study. The studies were classified in very low, low, moderate, and high quality according to study design, risk of bias (assessed by using the Newcastle–Ottawa Scale), consistency, directness, precision, publication bias, effect, confounders, and spurious effect (Tables 1) .

Potential selection bias of the included studies

The outcomes of patients hospitalized for COVID-19 disease depend on the emergency status of the health systems of the included studies, the period of the study (with worse outcomes in the first waves of the pandemic), and the selected population.

Outcomes

In the analysis on cardiovascular calcifications, only coronary calcifications were included due to the lack of data on aortic valve calcifications (reported in one study) and on thoracic aortic calcifications (reported in two studies but not comparable due to methodological limitations).

Based on the available outcomes of the included studies, the following end-points were assessed:

(1) Impact of coronary calcifications (expressed differently in different studies) on mortality
(2) Impact of coronary calcifications on the respiratory outcome "Orotracheal intubation"
(3) Impact of coronary calcifications on MACE (defined as a composite endpoint of acute coronary syndrome, stroke, and pulmonary embolism)

Statistical analysis

Quantitative data are reported as mean and standard deviation or median value with interquartile range. The categorical data are reported in percentages.

The available data were analyzed using OpenMetanalyst, a completely open-source, cross-platform software for advanced meta-analysis and with STATA version 13. The results are expressed in terms of odds ratio (OR) with a 95% confidence interval. Meta-analysis pooling of odds ratios was performed with the random-effects inverse-variance model. For the age, sex, and diabetes covariates, meta-regression was performed again with the random-effects model. The heterogeneity of the results was evaluated with the I squared index reported as a percentage. The association between categorical variables (calcium score and outcomes) was expressed in terms of odds ratios (OR).

Results of the systematic review

After an examination of titles, abstracts, and full texts for eligibility and having excluded all the items which did not respect inclusion and exclusion criteria and duplicate records, 11 papers were included in the meta-analysis [11–21].

The characteristics of each study are shown in Table 1. The quality of evidence assessment for each study is shown in the last column. None of the studies reached the highest level of quality, in part explained by the absence of randomized trials conducted to date on this topic.

Results of the meta-analysis

The systematic search and meta-analysis included 2875 patients from 11 studies (see Table 1) reporting CAC scoring and hospital outcomes of patients. Only 6 out of 11 studies had a sample size greater than 100 patients.

The mean age of the population included in the meta-analysis was 62 years, 35% of patients were female, 57% were hypertensive, and 31% were diabetic (data in line with the COVID-19 literature of hospitalized patients).

628 of 2775 patients died, with an average mortality of 20.7% (95% CI 12.5–28.9; I^2 p value < 0.001) (Fig. 1).

Mortality of the included studies ranged from the lowest value of 4.3% (Dillinger et al.) to the greatest value of 45.7% in the study by Fervers et Al.

Table 1 Summary table of studies included in the systematic review: first author, publication date, study country, publication journal, sample size, study design, and main results are reported

Authors (date of publication), country	Title. *Journal of publication*	Sample size (N)	Study design	Variable-outcome	Main findings	Mortality	Quality of evidence
Colombi et al. (October 2020), Italy	Qualitative and quantitative chest CT parameters as predictors of specific mortality in COVID-19 patients *Emergency Radiology*	248	Retrospective	V-CACS—In-hospital mortality	V-CACS > 1 (HR 2.76–3.32, P < 0.01/P < 0.001) associated with shorter overall survival	78/248 (31.5%)	Low
Cosyns et al. (December 2020), Belgium	Coronary Calcium Score in COVID-19 Hospitalized Patients *Journal of the American College of Cardiology—Cardiovascular Imaging*	280	Retrospective	CACS—Composite endpoint (mechanical ventilation, extracorporeal membrane oxygenation, or death within 30 days following hospital admission)	CACS predicted the endpoint, but adjusting for age was nonsignificant ($P = 0.128$)	45/280 (16%)	Very low
Dillinger et al. (November 2020), France	Coronary Artery Calcification and Complications in Patients With COVID-19 *Journal of the American College of Cardiology—Cardiovascular Imaging*	209	Cross-sectional	CAC—Composite endpoint (mechanical ventilation, extracorporeal membrane oxygenation, or death within 30 days following hospital admission)	Primary outcome in 50.0% of CAC + patients vs. 17.5% of CAC − patients ($P < 0.0001$). CAC is independently associated with the primary outcome (HR: 4.4, $P < 0.0001$)	30/209 (14.4%)	Low
Fervers et al. (December 2020), Germany	Calcification of the thoracic aorta on low-dose chest CT predicts severe COVID-19 *PLOS One*	70	Retrospective	AWC—COVID-19 severity	Higher AWC volume with severe COVID-19, compared to moderate cases (771.7 mm3 IQR 49.8–3065.5 mm3 vs. 0 mm3 IQR 0–57.3 mm3). AWC volume significant regressor for severe COVID-19 ($P = 0.004$) (multivariate regression)	32/70 (45.7%)	Low
Fovino et al. (July 2020), Italy	Subclinical coronary artery disease in COVID-19 patients *European Heart Journal—Cardiovascular Imaging*	53	Retrospective	CACS—Composite endpoint (mortality and intensive care unit admission)	50% of patients with CACS ≥ 400 died during hospitalization vs. 8.9% with CACS < 400 ($P = 0.003$)	8/53 (15%)	Very low

Table 1 (continued)

Authors (date of publication), country	Title. *Journal of publication*	Sample size (N)	Study design	Variable-outcome	Main findings	Mortality	Quality of evidence
Giannini et al. (March 2021), Italy	Coronary and total thoracic calcium scores predict mortality and provide pathophysiologic insights in COVID-19 patients *Journal of Cardiovascular Computed Tomography*	1093	Retrospective registry	CAC, AVC, and TAC score and volume—In-hospital mortality	Higher coronary artery, aortic valve, and thoracic aorta calcium values in non-survivors vs. survivors. CAC (HR 1.308, $P=0.019$) and TAC (HR 1.975, $P=0.007$) independent predictors of in-hospital mortality	211/1093 (19.3%)	Moderate
Gupta et al. (February 2021), USA	Coronary artery calcification in COVID-19 patients: an imaging biomarker for adverse clinical outcomes *Clinical Imaging*	180	Retrospective cohort	CACS—Intubation and in-hospital mortality	CACS is associated with intubation (OR 3.6, CI 1.4–9.6) and mortality (OR 3.2, CI 1.4–7.9). Severe CAC independently associated with intubation (OR 4.0, CI: 1.3–13) and mortality (OR 5.1, CI 1.9–15). Greater CACS (OR 1.2, CI 1.02–1.3) and the number of vessels with calcium (OR 1.3, CI 1.02–1.6) are associated with mortality	59/180 (32.6%)	Low
Nair et al. (January 2021), Qatar	Utility of visual coronary artery calcification on non-cardiac gated thoracic CT in predicting clinical severity and outcome in COVID-19 *Clinical Imaging*	67	Retrospective	V-CACS—COVID-19 severity	V-CACS cut-off value of 3 is an independent predictor for clinical severity, the need for ICU admission, and assisted ventilation. V-CACS is an independent predictor of clinical severity in COVID-19 (OR 1.72, $P=0.05$)	3/67 (4.5%)	Low

Table 1 (continued)

Authors (date of publication), country	Title. *Journal of publication*	Sample size (N)	Study design	Variable-outcome	Main findings	Mortality	Quality of evidence
Shabbir et al. (May 2021), USA	Coronary artery calcification heralds adverse clinical outcomes in patients hospitalized for COVID-19 *Journal of the American College of Cardiology*	73	Retrospective	CACS—In-hospital mortality	CACS is significantly associated with acute coronary syndrome, respiratory failure, need for intensive care, acute kidney injury, and in-hospital mortality, but not an independent predictor for those outcomes on multivariate analysis	21/73 (28.8%)	Very low
Slipczuk et al. (March 2021), USA	Coronary artery calcification and epicardial adipose tissue as independent predictors of mortality in COVID-19 *The International Journal of Cardiovascular Imaging*	493	Retrospective, posthoc analysis	CACS-DRS—In-hospital mortality	Higher CAC-DRS (3 vs 1, $P<0.001$) in non-survivors. CAC-DRS ≥ 4 independent predictor of mortality with increased mortality of 63% ($P=0.003$)	197/493 (40%)	Low
Zimmermann et al. (December 2020), Germany	Coronary calcium scoring assessed on native screening chest CT imaging as a predictor for outcome in COVID-19: An analysis of a hospitalized German cohort. *PLOS One*	109	Retrospective	CACS—Moderate, critical, fatal outcome, a composite endpoint of the previous outcomes	Higher number of events with CACS above the median for critical outcome (HR 1.97, $P=0.026$), fatal outcome (HR 4.95, $P=0.041$) and the composite endpoint (HR 2.31, $P=0.005$. OR significantly increased for critical outcome (OR 3.01, $P=0.01$) and for the fatal outcome (OR 5.3, $P=0.02$)	11/109 (10.1%)	Low

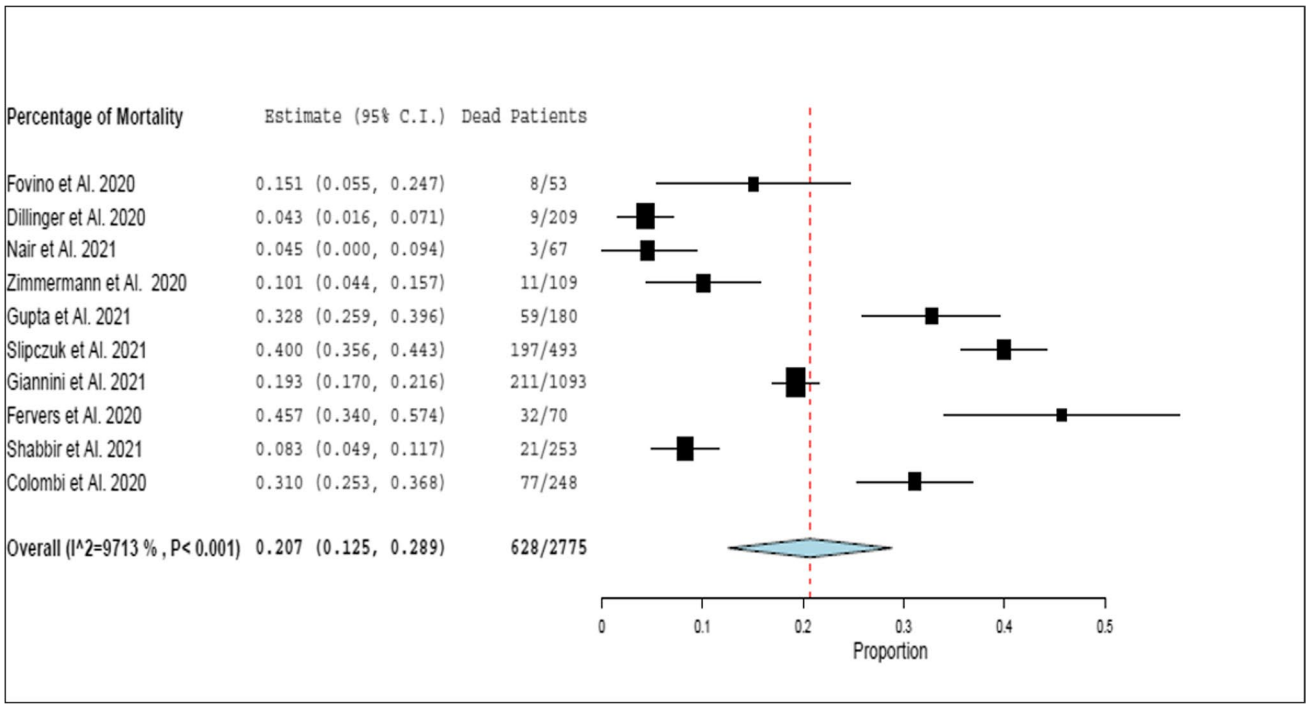

Fig. 1 Overall mortality in the studies included in the review

The I^2 statistic (p value < 0.001) of the mortality rate underlines the heterogeneity of the populations examined.

In meta-regression analyses for mortality, the mean age of the studies was positively associated with mortality (p value 0.016) (Fig. 2A).

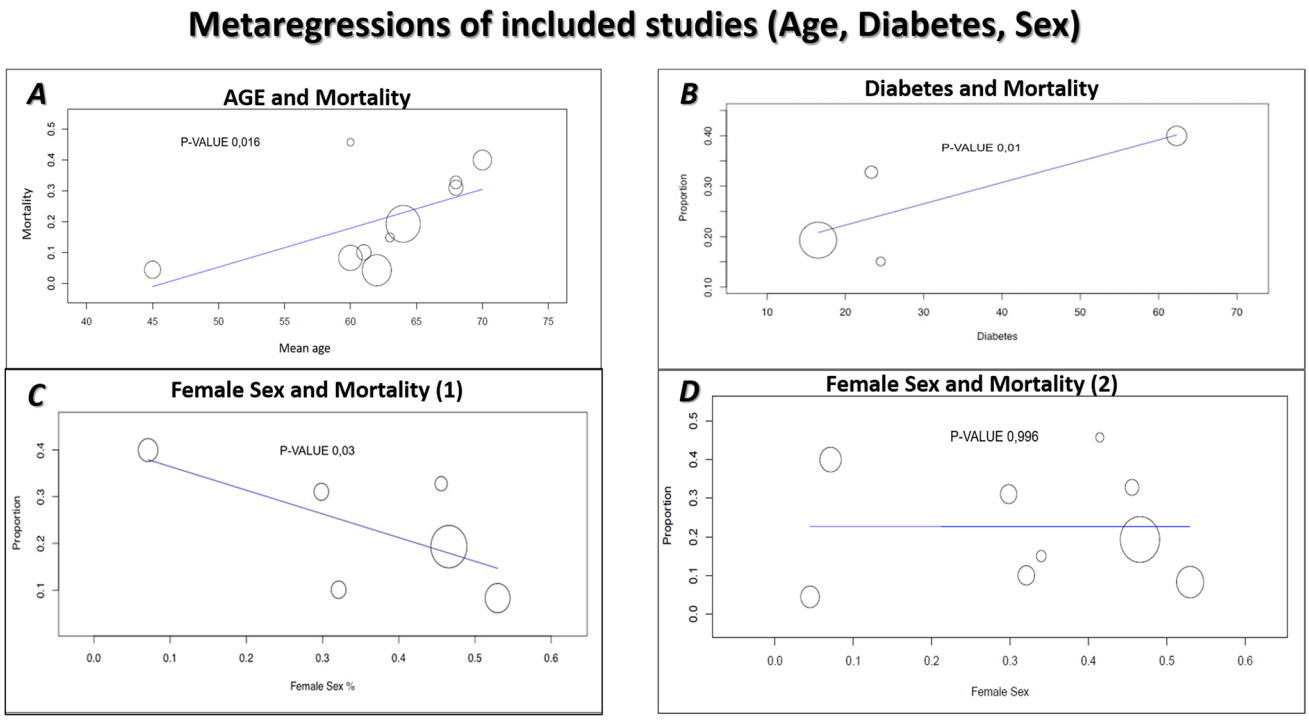

Fig. 2 A Meta-regression for mortality using the mean age of the included studies as a continuous covariate B. Meta-regression of mortality of the studies with the available prevalence data of diabetic patients. C. Meta-regression for mortality using female prevalence as a continuous covariate. D Meta-regression of mortality for the prevalence of female sex in the 5 studies with more than 100 patients

The sex covariate including all studies did not appear to be associated with mortality (Fig. 2C, D).

The prevalence of diabetes, available in only 4 studies, was positively associated with a higher mortality rate (Fig. 2B).

Patients with coronary calcifications (CAC > 0 vs. CAC = 0 patients) had a mortality OR of 2.19 (95% CI 1.36–2.52). Patients who did not have coronary calcium on chest CT had a 54% lower mortality risk (Fig. 3).

CAC of 0 was a strong negative risk factor and "de-risks" patients. COVID-19 patients without coronary calcifications were nearly 50% less likely to die (OR 0.46 0.28–0.74) (Fig. 3).

Patients with severe calcifications (defined as a CAC > 400mm3) had an even greater risk of death (OR 2.49 1.15–5.41) regardless of orotracheal intubation (OR 0.94 0.22–4) (Fig. 4). Respiratory outcome (orotracheal intubation) was independent of coronary calcifications (Fig. 5, OR 1.08 0–75-1.55).

Patients with severe calcifications (CAC > 400 mm3) had an increased risk of cardiovascular events (acute coronary syndromes, pulmonary embolism and stroke) with an OR of 1.73 (1.04–2.88) (Fig. 6). Analyzing mortality according to the CAD score- DRS, it is seen that with increasing severity of calcifications, there was an increase in mortality that reached 45.8% in patients with CAC-DRS 3 (Figs. 7–8).

In all mortality analyses, coronary calcifications (assessed as presence/absence or in quantitative terms) were correlated with an increased risk of mortality from COVID-19. The severity of coronary calcifications (expressed by the CAC-RAD classification in Fig. 9) was associated with higher mortality rates.

Discussion

The present systematic review and meta-analysis suggest that CAC is associated with mortality of COVID-19 patients; it is not related to the respiratory outcome of orotracheal intubation. Patients with more coronary calcific burden tend to have higher mortality, and the presence of CAC is associated with cardiovascular events (acute coronary syndrome, pulmonary embolism, and stroke).

In the various papers, various CAC score measurements (qualitative, quantitative, categorical quantitative, or comparisons through the median value of the population) were examined. This measurement heterogeneity limits the meta-analytic comparisons of the different studies, weakening the final result of the meta-analysis.

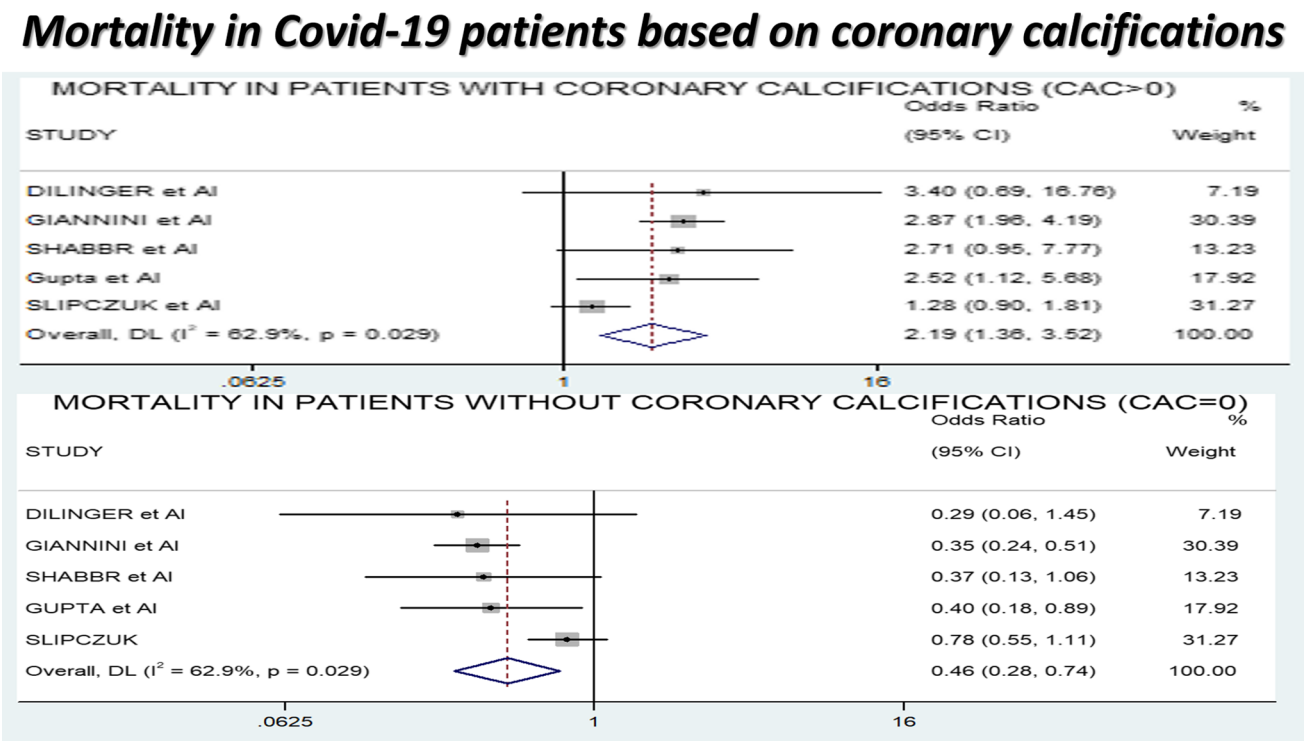

Fig. 3 Meta-analysis including studies with mortality for patients with coronary calcifications and without (zero coronary calcium). The graph above shows that coronary calcifications (coronary calcium score > 0) increase mortality due to COVID-19. The same data can be interpreted in the graph below in terms of the protective effect of the zero coronary calcium score on mortality in patients with COVID-19

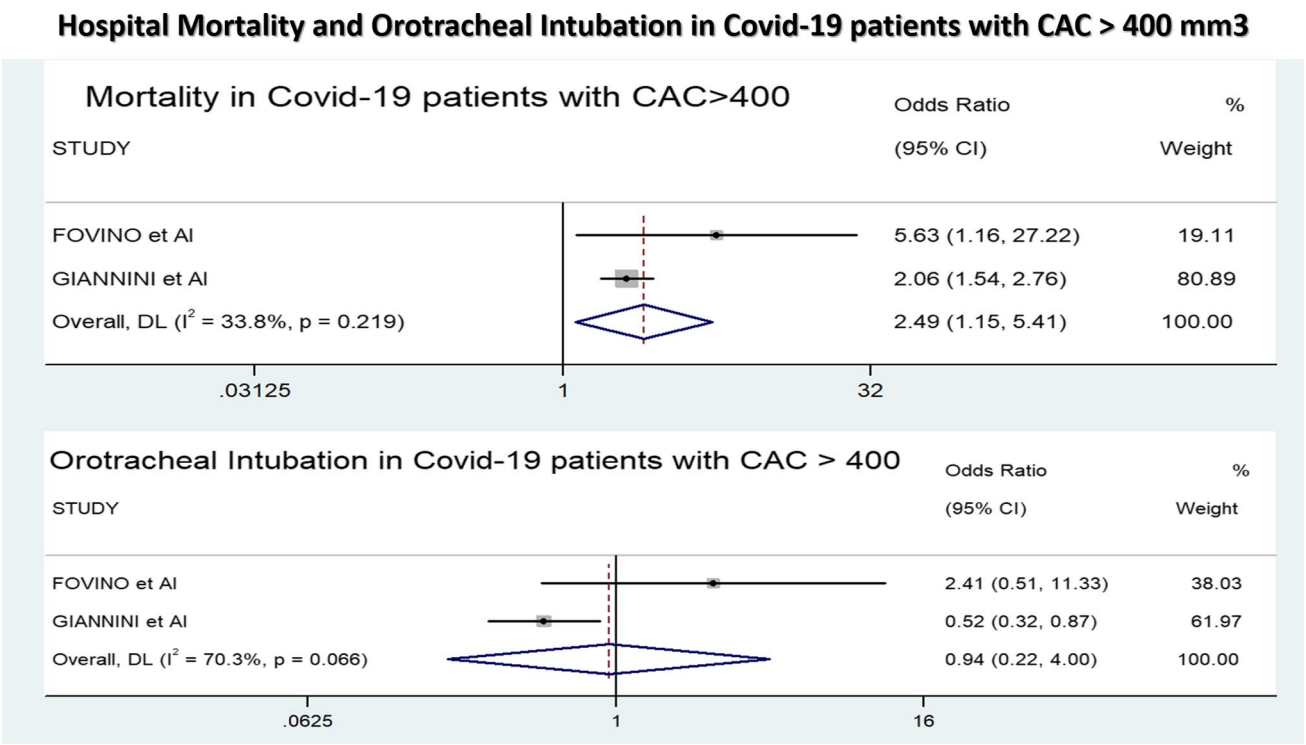

Fig. 4 Plot with the outcomes (mortality and intubation) in patients with coronary calcium score > 400. The above plot shows the mortality, the one below the intubation

CAC values often invalidate the predictive significance of other cardiovascular risk factors (such as hypertension and diabetes). On the contrary, in the stratification of the asymptomatic patient with intermediate risk for CAD (as the recommendation of the American guidelines with evidence class IIa), the value of the CACS is incremental and does not eliminate the significance of the other risk factors in the multivariate analyses.

This statistical overlapping of the calcium score with other risk factors is physiopathologically explainable because CAC is a cumulative marker of vascular damage caused by exposure to other cardiovascular risk factors.

Probably the significance of this overlapping can be explained from a statistical point of view with the collinearity between calcium score and cardiovascular risk factors.

Despite the collinearity bias [6], the CAC was predictive of death in the paper by Giannini et al. independently from age, sex, creatinine, and lung interstitial involvement [16].

It is also necessary to take into consideration that the populations are heterogeneous and representative of different pandemic

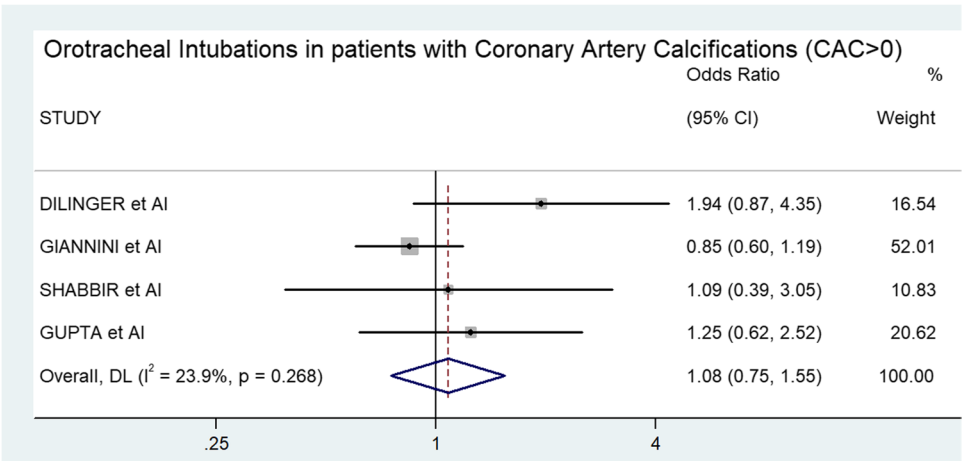

Fig. 5 Metanalytic plot of intubated patients with coronary calcifications vs. patients with a Coronary Calcium Score of zero

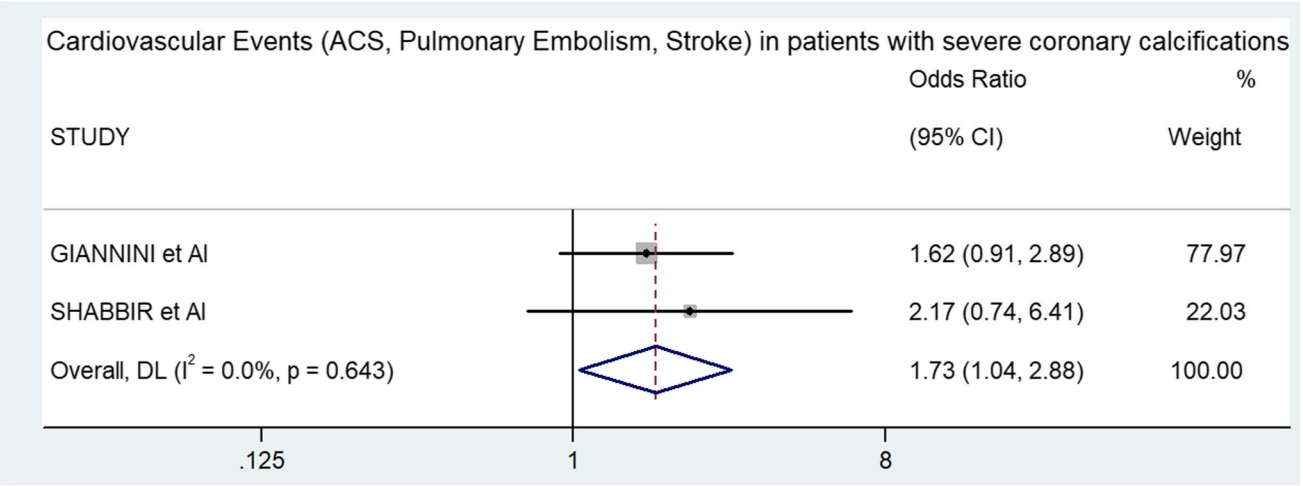

Fig. 6 Plot with MACEs (acute coronary syndrome, pulmonary embolism, stroke) in patients with coronary calcifications vs. patients with zero calcium score

phases and different health systems (with different diagnostic and therapeutic policies, especially as regards non-invasive ventilation and intubation). In the early pandemic waves, evidence on the use of heparin and steroids was not yet available.

There are three possible explanations for the predictivity of CAC death in COVID:

(1) The first cardiovascular hypothesis is that CAC is a more sensitive cardiovascular marker than other anamnestic variables (probably weakened by suboptimal data collection in retrospective studies). Coronary calcium score, being a cumulative marker of cardiovascular damage, includes all risk factors [22].

The CAC can therefore be considered as a cumulative measure of cardiovascular damage with different degrees of severity even in the asymptomatic patient. In a disease that has a marked cardiovascular tropism, having a low

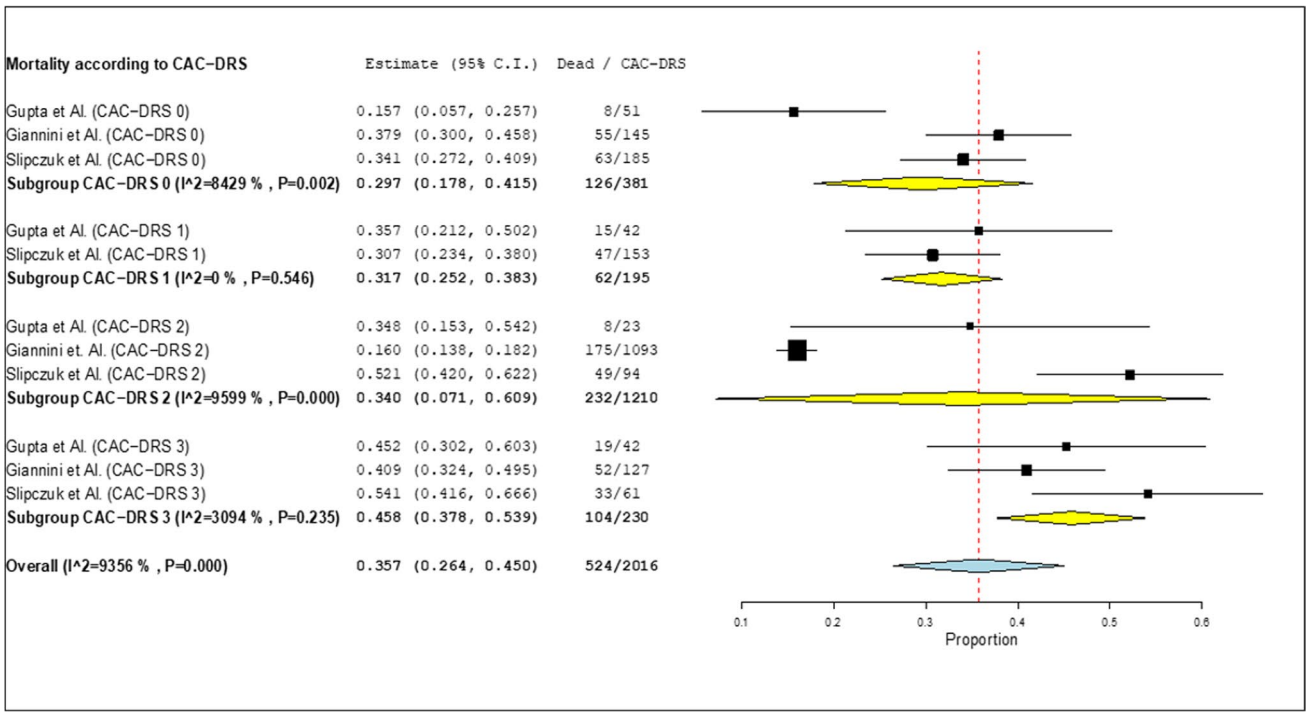

Fig. 7 Meta-analysis subgroups for the visual value of CAD-RDS (0, 1, 2, 3)

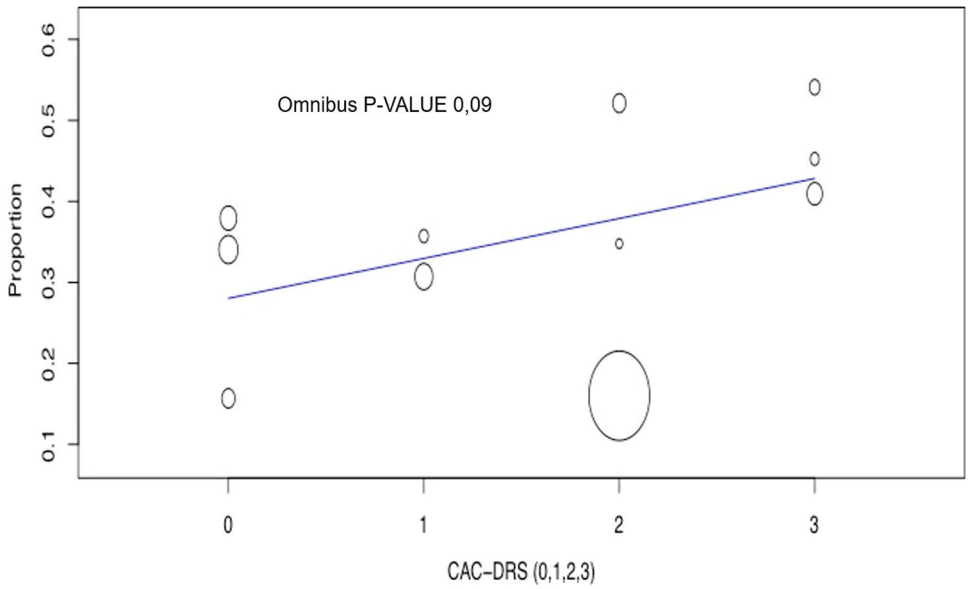

Fig. 8 Mortality meta-regression of studies by CAC-RDS subgroups

calcium score probably confers some sort of resilience to Sars-CoV2 infection.

It is also presumed that the patient with cardiovascular calcifications has a greater activation of the RAAS system which favors viral replication and vascular damage.

(2) We can then suppose the existence of a second hypothesis that sees the calcium score as a marker of fragility [23].

Cardiovascular disease is associated with frailty, and frailty increases the risk of adverse outcomes in patients with cardiovascular disease.

Older patients, with more comorbidities, have higher CAC values and are more exposed to complications of SARS-CoV2 disease, with higher mortality. The patient with a higher calcific burden is frailer and more exposed to type II myocardial damage secondary to respiratory hypoxia [24].

In a disease with cardiovascular tropism, cardiovascular calcifications could indirectly represent the cardiovascular health of the individual (independently of other anamnestic and laboratory variables), and their quantification allows evaluating the cardiovascular resilience to Sars-CoV2.

(3) The third hypothesis is the "immunological" one. Since CAC is related to epicardial adipose Tissue (EAT), we can assume that these patients have a higher baseline cardiometabolic inflammatory phenotype. These patients have a more pronounced basal inflammatory response that exposes them more to the cytokine storm induced by Sars-CoV2 [20]. It is well known that atherosclerotic disease is also associated with immune system dysregulation and a chronic inflammatory state.

Interestingly, in predominantly respiratory disease, CAC is neutral in terms of respiratory outcomes such as orotracheal intubation.

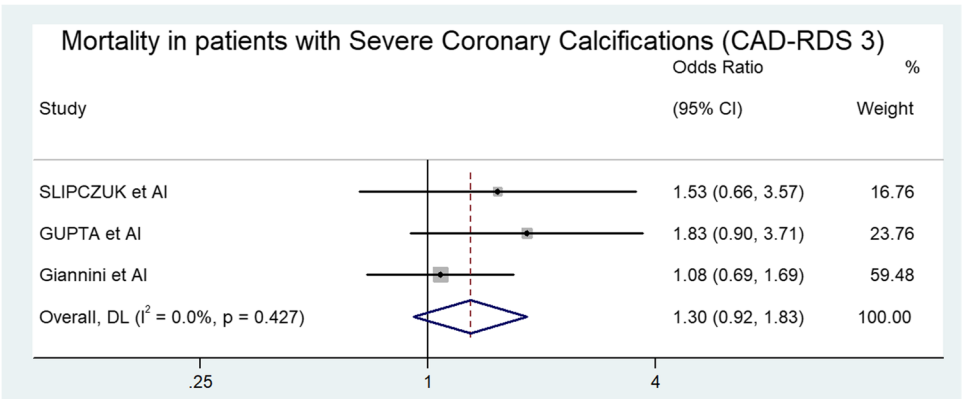

Fig. 9 Meta-analysis of the mortality of patients with CAC-DRS 3 versus those with CAC-DRS 0–1 (Severe vs. Absent Mild Coronary Calcifications)

The association between MACEs and CAC on the other hand is easier to explain.

Patients who have the most coronary plaque burden are also those most exposed to plaque rupture with multiple coronary and stroke syndromes.

The pathogenesis of the pulmonary thromboembolic event is instead sought in a greater inflammatory/coagulative response of patients with elevated CAC [12].

Sars-CoV2 (like any infectious state) can favor the erosion/rupture of plaques and favor thromboembolic events and therefore increase the probability of cardiovascular events.

The CAC, despite methodological limitations, nevertheless appears as a promising imaging marker in COVID-19.

It is an easy-to-use imaging biomarker, does not take too long to measure, and could be an added value compared to pulmonary findings.

However, the validity of this marker will have to be validated by the large numbers of clinical trials (where often the basal lung CT was an inclusion criteria).

The CAC score values in drug trials could also tell us whether patients with coronary calcifications respond better or worse to specific therapies (such as heparin, steroids, or monoclonal antibodies).

Future research perspectives

The calcium score, in the perspective of cardiovascular risk stratification, is probably "the elephant in the room" and it is often overlooked in radiological reports.

CAC is the most reliable element in cardiovascular risk stratification in terms of precision of predictive ability and CAC of 0 is a strong negative risk factor and "de-risks" patients.

If CAC is predictive of death in a new and not classically cardiovascular disease, let us think about its potential innovative applications in cardio-oncology and patients with end-stage nephropathy [25].

The non-cardiovascular application of this bioimaging marker could reclassify the risk profile of millions of patients who perform pulmonary CT every year for other clinical reasons.

Conclusion

From the following meta-analysis of 11 studies, the role of coronary calcium score appears evident in terms of mortality prediction despite bias and heterogeneity.

Coronary calcium in the studies included in this systemic review and meta-analysis was significantly associated with mortality. It was found to be neutral in terms of respiratory outcomes and showed a trend towards a greater number of MACEs.

However, routine reporting of the CAC score on non-contrast chest CT, regardless of clinical indication (COVID-19 lung disease staging, pulmonary embolism, or other respiratory complications), promotes early diagnosis of subclinical atherosclerosis and stratifies the risk of COVID-19 patients [26, 27].

Declarations

Conflict of interest The authors declare no competing interests.

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