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Impact of clinical and subclinical coronary artery disease as assessed by coronary artery calcium in COVID-19

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ABSTRACT

Background and aims: The potential impact of coronary atherosclerosis, as detected by coronary artery calcium, on clinical outcomes in COVID-19 patients remains unsettled. We aimed to evaluate the prognostic impact of clinical and subclinical coronary artery disease (CAD), as assessed by coronary artery calcium score (CAC), in a large, unselected population of hospitalized COVID-19 patients undergoing non-gated chest computed tomography (CT) for clinical practice.

Methods: SARS-CoV 2 positive patients from the multicenter (16 Italian hospitals), retrospective observational *SCORE COVID-19* (calcium **s**core for **CO**VID-19 **R**isk **E**valuation) registry were stratified in three groups: (a) "clinical CAD" (prior revascularization history), (b) "subclinical CAD" (CAC >0), (c) "No CAD" (CAC = 0). Primary endpoint was in-hospital mortality and the secondary endpoint was a composite of myocardial infarction and cerebrovascular accident (MI/CVA).

Results: Amongst 1625 patients (male 67.2%, median age 69 [interquartile range 58–77] years), 31%, 57.8% and 11.1% had no, subclinical and clinical CAD, respectively. Increasing rates of in-hospital mortality (11.3% *vs.*

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27.3% *vs.* 39.8%, $p < 0.001$) and MI/CVA events (2.3% *vs.* 3.8% *vs.* 11.9%, $p < 0.001$) were observed for patients with no CAD *vs.* subclinical CAD vs clinical CAD, respectively.
The association with in-hospital mortality was independent of in-study outcome predictors (age, peripheral artery disease, active cancer, hemoglobin, C-reactive protein, LDH, aerated lung volume): subclinical CAD *vs.* No CAD: adjusted hazard ratio (adj-HR) 2.86 (95% confidence interval [CI] 1.14–7.17, p=0.025); clinical CAD *vs.* No CAD: adj-HR 3.74 (95% CI 1.21–11.60, p=0.022). Among patients with subclinical CAD, increasing CAC burden was associated with higher rates of in-hospital mortality (20.5% *vs.* 27.9% *vs.* 38.7% for patients with CAC score thresholds≤100, 101–400 and > 400, respectively, $p < 0.001$). The adj-HR per 50 points increase in CAC score 1.007 (95%CI 1.001–1.013, p=0.016). Cardiovascular risk factors were not independent predictors of in-hospital mortality when CAD presence and extent were taken into account.
Conclusions: The presence and extent of CAD are associated with in-hospital mortality and MI/CVA among hospitalized patients with COVID-19 disease and they appear to be a better prognostic gauge as compared to a clinical cardiovascular risk assessment.

1. Introduction

Since December 2019, SARS-CoV-2, the causative agent of the ongoing coronavirus disease 2019 (COVID-19) pandemic, has infected more than 118 million people worldwide. The number of affected individuals is continuing to escalate, which places a significant burden upon national healthcare systems. In this context, precise prognostication to optimize resource allocation and patient management is of utmost importance. Furthermore, understanding the pathophysiological reasons for adverse prognosis in COVID-19 disease may aid the development of patient specific management strategies.

Several predictors of COVID-19-related mortality have been described, including patient comorbidities, clinical, radiological and ultrasound features of lung disease severity and serum biomarkers of inflammation and organ damage [1]. The presence of cardiovascular risk factors and previous comorbidities in patients with COVID-19 disease is associated with adverse outcomes and higher in-hospital mortality [2–4].

However, the pathophysiological link between clinical cardiovascular risk factors and outcomes in COVID-19 remains largely unexplored. In this regard, atherosclerotic disease may be a substratum of more severe COVID-19 disease manifestations. As a disconnection exists between the cardiovascular clinical risk and the actual presence of atherosclerosis [5,6], coronary artery calcium (CAC), a highly specific marker of atherosclerotic burden [7], may be a better gauge of COVID-19 outcomes than clinical profile. This hypothesis seems to be supported by some recent small, single center exploratory studies [8–10].

We tested the hypothesis that combining clinical history details with CAC score on routine non gated chest computed tomography (CT) could better explore the spectrum of coronary artery disease (CAD) and stratify prognosis amongst patients admitted with COVID-19.

2. Patients and methods

2.1. Study design and population

SCORE COVID-19 (calcium **s**core for **CO**VID-19 **R**isk **E**valuation) is a multicenter, retrospective, observational registry comprising 1691 SARS-CoV 2 positive consecutive patients admitted to 16 Italian hospitals between March 1, 2020 to April 24, 2020 with an available non-contrast chest CT scan performed for pneumonia severity assessment. Of 1691 patients, 66 were excluded (6 for missing CT images, 32 because of no computable CAC score, 27 for missing outcome data) leading to a final population of 1625 patients.

Demographic characteristics, cardiovascular risk factors, along with clinical, laboratory and chest CT imaging variables related to the index hospitalization were collected in a dedicated pre-specified dataset by each center and analyzed by the coordinating center (Maria Cecilia Hospital, GVM Care & Research, Cotignola, Italy).

The diagnosis of COVID-19 disease was established by a positive qualitative polymerase-chain-reaction assay for SARS-CoV-2. Chest CT scans were acquired with a standard non-gated chest CT protocol, on multidetector scanners with at least 16 detector rows. Imaging data were collected by each center and sent to the central core-lab for image analysis (Experimental Imaging center, IRCCS, Ospedale San Raffaele, Milano) by three expert cardio-thoracic radiologists of the core-lab blinded to patients clinical data. The presence and vessel location (left main, left anterior descending, left circumflex or right coronary artery) of calcification was visually assessed if CAC was detected, the Agatston CAC score was quantitatively computed with a validated commercial software (IntelliSpace v 8.0 software, Philips, The Netherlands).

For the purpose of this analysis, COVID-19 patients were stratified into three groups as follows: (a) "clinical CAD" as defined by a history of previous surgical or percutaneous coronary revascularization, (b) "subclinical CAD" as defined by a CAC >0, (c) "No CAD" as defined by a CAC = 0.

Patient with subclinical CAD were further stratified according to validated CAC score thresholds (≤100: mild; 100–400: moderate; >400: severe) [10]. Sensitivity analyses for age groups were also performed.

2.2. Study endpoints

The primary endpoint was in-hospital mortality.

The secondary endpoint was a composite of in-hospital myocardial infarction and cerebrovascular accident (MI/CVA).

Study outcomes were retrospectively ascertained by a physician at each participating center, who reviewed all the medical records. MI was defined according the Fourth Universal definition of Myocardial infarction [11], while the diagnosis of CVA was assessed according to clinical practice.

2.3. Statistical analysis

Categorical variables are expressed as number and percentages, continuous variables are expressed as mean ± standard deviation or median and interquartile range (IQR) as appropriate. Unpaired *t*-test or nonparametric Mann-Whitney *U* test was used for comparisons of continuous variables and chi-square test was used for categorical variables. Kaplan-Meier curves were performed to evaluate cumulative event rates at follow-up. Log-rank *p*-value was determined to test if Kaplan Meier event estimates differed over time. Outcomes were then adjusted with a multivariate Cox proportional hazards model. All baseline variables presented in Tables 1 and 2 were tested for univariate significance. Those found to be significantly associated with the primary outcome in univariable models ($p < 0.05$) were included in the final Cox regression model, provided that they had less than 30% missing data. The proportional hazards assumption of the Cox regression model was

Table 1
Clinical and laboratory characteristics of the overall population and stratified by CAD categories.

	Total (n) (N = 1625)	No CAD (N = 504)	Subclinical CAD (N = 940)	Clinical CAD (N = 181)	*p*-value
Clinical characteristics					
Age [IQR] (n)	69 [58, 77] (1625)	57 [50, 66] (504)	72 [63, 79] (940)	75 [69, 81] (181)	<0.001
Male gender % (n)	67.2 (1092)	55.2 (276)	70.9 (666)	81.1 (150)	<0.001
BMI [IQR] (n)	26 [24 29] (560)	26 [24, 29] (208)	27 [24, 29] (297)	26 [23, 28] (55)	0.191
Hypertension % (n)	54.8 (885)	34.3 (171)	60.4 (565)	82.3 (149)	<0.001
Diabetes % (n)	19.1 (309)	7.8 (39)	21.3 (199)	39.2 (71)	<0.001
Smoke % (n)	6.5 (79)	3.7 (15)	6.8 (46)	13.4 (18)	<0.001
CKD % (n)	7.3 (87)	2.3 (9)	7.2 (49)	23.4 (29)	<0.001
Atrial fibrillation % (n)	9 (140)	3.5 (17)	10.1 (90)	18.3 (33)	<0.001
Peripheral artery disease %(n)	6.1 (98)	1.4 (7)	6 (56)	19.3 (35)	<0.001
Chronic lung disease % (n)	9.9 (160)	5 (25)	11.3 (106)	16 (29)	<0.001
Active malignancy % (n)	5.1 (83)	3 (15)	5.9 (55)	7.2 (13)	0.009
Laboratory data at admission					
Hb g/dl [IQR] (n)	14 [12,15] (1617)	14 [12, 15] (501)	14 [12, 15] (936)	13 [12, 15] (180)	0.580
WBC*10^3/mm^3 [IQR] (n)	6.8 [5.0, 9.9] (1548)	6.2 [4.7, 9.2] (485)	7.1 [5.3, 10.1] (884)	7.3 [5.2, 10.6] (179)	<0.001
Creat. Mg/dL [IQR] (n)	1.0 [0.9, 1.2] (324)	1.0 [0.8, 1.1] (115)	1.0 [0.9, 1.2] (177)	1.1 [1.0, 1,6] (32)	<0.001
HS-TnI ng/L baseline [IQR] (n)	10.9 [5.4, 32.9] (275)	6.0 [2.7, 15.0] (91)	10.9 [6.0, 35.5] (140)	32.8 [14.8, 93.0] (44)	<0.001
HS-TnI ng/L peak [IQR] (n)	10.9 [5.4, 32.9] (265)	9.9 [4, 31] (87)	19.5 [9, 59.1] (140)	53.1 [22.5, 150.1] (38)	<0.001
LDH mg/dl [IQR] (n)	354 [254, 480] (1140)	330 [240, 442] (357)	365 [264, 495] (665)	350 [252, 463] (118)	0.010
CRP mg/L [IQR] (n)<	11.5 [5.3, 20] (1594)	10.5 [4.2,20.3] (486)	10.9 [5.6, 20.1] (929)	11.7 [6.6, 18.4] (179)	0.070

BMI = body mass index, Creat. = creatinine, CKD = chronic kidney disease, CR*P*=C-reactive protein, Hb = haemoglobin, IQR = interquartile range, LDH = lactate dehydrogenase, HS-TnI = high-sensitivity troponin I, WBC = white blood cells.

Table 2
Clinical and laboratory characteristics of patients with subclinical CAD stratified by increasing CAC burden.

	CAC <100 (N = 465)	CAC 100–400 (N = 219)	CAC ≥ 400 (N = 256)	*p*-value
Age [IQR] (n)	67.5 [60, 75] (465)	73 [66, 80] (219)	77 [71, 83] (256)	<0.001
Male gender % (n)	66.8 (310)	71.9 (156)	78.1 (200)	0.003
BMI - median [IQR] (n)	27 [25, 29] (151)	27 [24, 29] (68)	26.6 [25, 29] (78)	0.678
Arterial hypertension % (n)	60.5 (565)	59.9 (130)	65.9 (168)	0.040
Diabetes % (n)	21.3 (199)	24.0 (52)	27.1 (69)	<0.001
Smoker % (n)	6.8 (46)	5.7 (9)	8.5 (16)	0.412
Chronic kidney disease % (n)	7.2 (49)	8.8 (14)	9.3 (17)	0.002
Atrial fibrillation % (n)	10.1 (90)	8.1 (17)	14.2 (35)	0.050
Peripheral artery disease % (n)	6.0 (56)	6.0 (13)	10.6 (27)	<0.001
Chronic lung disease % (n)	11.4 (106)	11.1 (24)	14.1 (36)	0.103
Active malignancy % (n)	5.9 (55)	6.0 (13)	8.6 (22)	0.070
Laboratory data at admission				
Hemoglobin g/dl [IQR] (n)	14 [12, 15] (463)	13.9 [12, 15] (218)	13.3 [12, 15] (255)	0.320
WBC*10^3/mm^3 [IQR] (n)	7.1 [5.3, 9.7] (430)	6.9 [5.0, 9.9] (210)	7.1 [5.4, 10.6] (244)	0.280
Creatinine mg/dL [IQR] (n)	1.0 [0.8, 1.1] (97)	1.0 [0.9, 1.3] (34)	1.1 [0.9, 1.4] (46)	0.250
HS-TnI baseline ng/L [IQR] (n)	10.0 [6.0, 29.1] (60)	8.8 [5.3, 35.0] (34)	15.5 [7.2, 37.4] (46)	0.365
LDH mg/dl [IQR] (n)	392 [274, 520] (338)	342 [252, 473] (158)	360 [258, 462] (203)	0.780
CRP mg/L - [IQR] (n)	23 [13.3, 55.8] (460)	28.6 [15.5,61.2] (214)	29.1 [16.3, 68.5] (255)	0.390
HS-TnI ng/L peak [IQR] (n)	17.0 [8.5, 49.0] (74)	21.0 [8.5, 48.9] (31)	34.9 [13.6, 74.8] (35)	0.110

BMI = body mass index, Creat. = creatinine, CKD = chronic kidney disease, CRP=C-reactive protein, Hb = haemoglobin, IQR = interquartile range, LDH = lactate dehydrogenase, HS-TnI = high-sensitivity troponin I, WBC = white blood cells.

checked using time-dependent Cox models. Results are presented as hazard ratio (HR) with 95% confidence interval (CI). We assessed multicollinearity among the variables included in the final multivariate model by calculating the variance inflation factor (VIF). VIFs are reported in Supplementary Table 1 and were below 5 for all the independent variables suggesting no significant multicollinearity. Receiver Operating Characteristic (ROC) curves were elaborated for several predictive models and their associated areas under the curve (AUCs) were compared with DeLong et al. approach [12].

A $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using SPSS (version 24.0, SPSS Inc., Chicago, Illinois, US).

3. Results

3.1. Baseline characteristics

Amongst 1625 COVID-19 patients, 181 (11.1%) had a history of prior surgical or percutaneous revascularization (clinical CAD). Of the remaining 1444 patients, 940 (57.8%) were diagnosed with subclinical CAD and 504 (31%) had no evidence of CAC on chest CT.

Demographic, clinical and laboratory features stratified by CAD status are presented in Table 1. Overall, median age was 69 years [IQR 58, 77], 67.2% were males. Older age, higher burden of cardiovascular comorbidities including arterial hypertension, diabetes, smoke, atrial fibrillation and peripheral artery disease along with more frequent male sex and chronic kidney and lung diseases were observed across the spectrum from No CAD to clinical CAD. The same increasing trend across the groups was also observed for laboratory data at admission, including white blood cell count, creatinine level, high-sensitivity Troponin I (hs-TnI) at admission and at peak.

3.1.1. Patients with subclinical CAD stratified by CAC burden

Demographic and clinical characteristics of patients with subclinical CAD stratified by CAC burden are presented in Table 2. Increasing CAC burden was associated with male sex, older age and higher rates of hypertension, diabetes, peripheral artery disease and chronic kidney disease.

Table 3
Independent predictors of in-hospital mortality at Cox regression analysis.

Variables	Multivariate analysis	
	HR (95% CI)	*p*-value
Age	1.07 (1.04–1.1)	**0.000**
Sex	0.71 (0.38–1.31)	**0.267**
Arterial hypertension	0.66 (0.38–1.13)	0.131
Diabetes	1.3 (0.76–2.21)	0.343
Smoke	0.94 (0.38–2.3)	0.890
Chronic lung disease	1.01 (0.47–2.14)	0.986
Peripheral artery disease	2.03 (1.19–3.67)	**0.02**
Atrial fibrillation	2.01 (0.96–4.24)	0.065
Active malignancy	2.9 (1.33–6.34)	**0.007**
Chronic kidney disease	1.56 (0.79–3.04)	0.198
Hemoglobin	1.15 (1.01–1.30)	**0.038**
WBC[a] $10^3/mm^3$ [IQR]	1.0 (1.0–1.0)	0.745
LDH (U/L)	1.0 (1.0–1.0)	0.002
CRP (m)	1.01 (1.0–1.01)	0.038
$SatO_2$ in AA	1.01 (0.98–1.03)	0.687
Clinical CAD[a]	3.74 (1.21–11.60)	**0.022**
Subclinical CAD[a]	2.86 (1.14–7.17)	**0.025**
Well aerated lung volume [cc]	0.999 (0.999–1.00)	**0.001**
Pericardial effusion	1.27 (0.62–2.6)	0.523
Pleural effusion	0.84 (0.48–1.47)	0.532
Pneumonia	0.91 (0.62–1.0)	0.244

HR = hazard ratio, CAD = coronary artery disease, CRP=C-reactive protein, LDH = lactate dehydrogenase, Sat O_2 in AA = oxygen saturation in ambient air.
[a] *vs.* No CAD. All the listed variables are univariate predictors of in-hospital mortality, the *p*-values refer to the final level of significance in the Cox multivariate model.

3.2. Study outcomes

3.2.1. Overall population

After a mean follow-up of 14 (10) days, in-hospital death occurred in 385 (23.7%) patients while in-hospital MI/CVA in 39 (2.4%) patients.

Increasing rates of in-hospital mortality (57 [11.3%, 0.8% person-day] *vs.* 256 [27.3%, 1.7% person-day] *vs.* 72 [39.8%, 2.9% person-day], $p < 0.001$) and MI/CVA (7 [2.3%, 0.1% person-day] *vs.* 20 [3.8%, 0.3% person-day] *vs.* 12 (11.9%, 0.9% person-day), $p < 0.001$) were observed for patients with No CAD *vs.* subclinical CAD *vs.* clinical CAD, respectively. Univariate predictors of the primary endpoint are presented in Supplementary Table 2.

In a Cox multivariate model with demographics and in-study outcome predictors (Table 3), "CAD stratification" was identified as an independent predictor of in-hospital mortality: subclinical CAD *vs.* No CAD: HR 2.86 95% CI 1.14–7.17, p=0.025; clinical CAD *vs.* No CAD: HR 3.74 95% CI 1.21–11.60, p=0.022 (Fig. 1), while no cardiovascular risk factor remained significantly associated with in-hospital mortality. A multivariate model with CAC as a continuous variable tested in patients with no CAD and subclinical CAD showed consistent results (Supplementary Table 4).

A multivariate model including "CAD stratification" was superior to a model based on clinical cardiovascular risk profile exclusively (AUCs: 0.71, 95%CI 0.66–0.76 *vs.* 0.62, 95%CI 0.56–0.68, *p*-value for AUCs comparison = 0.028) (Supplementary Table 4 and Supplementary Fig. 1). The final model, which included comorbidities and markers of COVID-19 disease severity, was superior to the model based on clinical cardiovascular risk profile and "CAD stratification" (final model AUC: 0.87, 95%CI 0.83–0.90, *p*-value for AUCs comparison <0.001). Despite being an independent predictor of the primary outcome, "CAD stratification" did not provide incremental prognostic value in terms of AUC to the full model of in-study outcome predictors including markers of COVID-19 disease severity (*p*-value for AUCs comparison = 0.933) (Supplementary Fig. 1).

3.2.2. Patients with subclinical CAD stratified by CAC burden

Among patients with subclinical CAD, increasing CAC burden was associated with higher rates of in-hospital mortality (20.5% *vs.* 27.9% *vs.* 38.7% for patients with mild, moderate and severe CAC, respectively, $p < 0.001$) also after multivariate adjustment (adj-HR per 50 points CAC increase: 1.007, 95%CI 1.001–1.013, p=0.016). A trend for higher rates of MI/CVA was also noted (2.5% *vs.* 4.5% *vs.* 5.4%, p=0.106) (Fig. 2). Similar results were observed when patients with subclinical CAD were stratified by the presence *vs.* absence of left main coronary artery

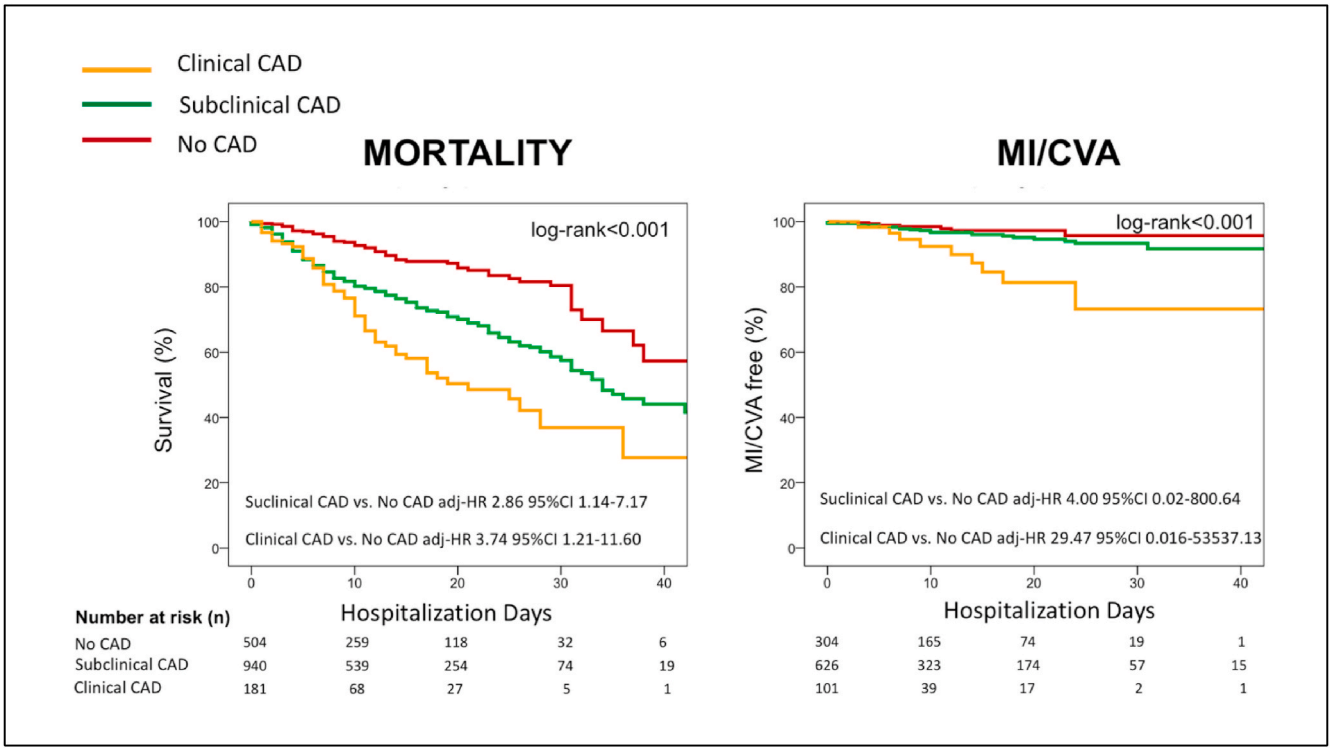

Fig. 1. Kaplan Meyer estimates of in-hospital mortality and a composite of in-hospital myocardial infarction and cerebrovascular accident stratified by CAD status.

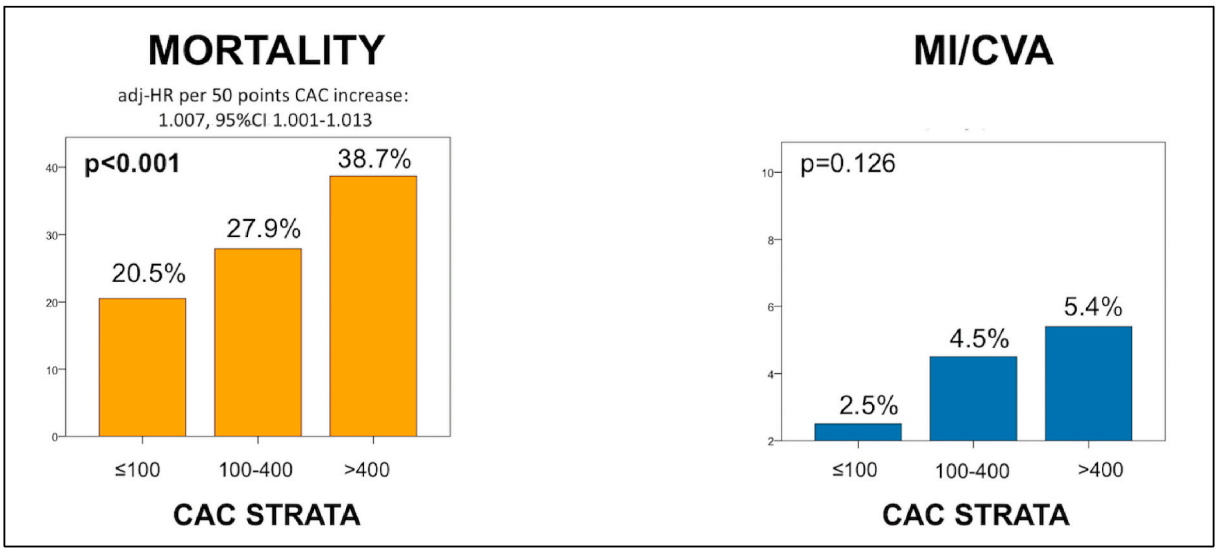

Fig. 2. In-hospital mortality and a composite of in-hospital myocardial infarction and cerebrovascular accident as stratified by increasing CAC burden.
Adjusted hazard ratio for demographics and in-study outcome predictors is provided for the primary endpoint. CAC = coronary artery calcium; HR = hazard ratio, MI/CVA = myocardial infarction/cerebrovascular accident.

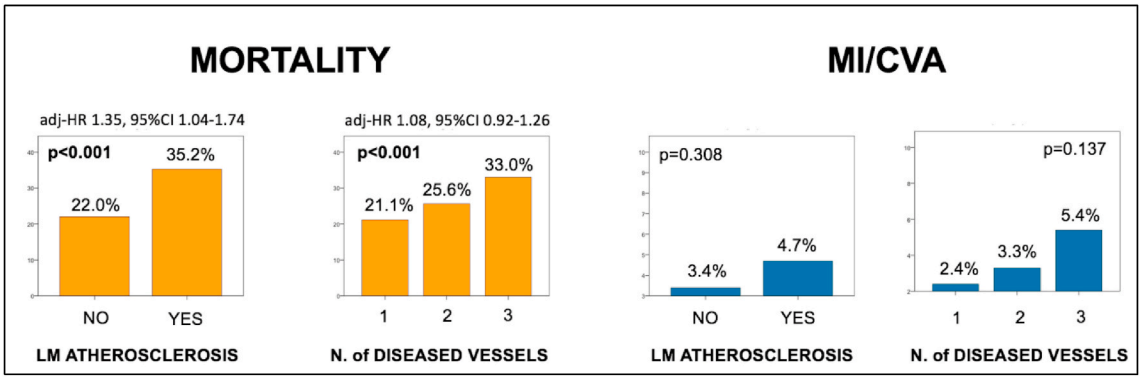

Fig. 3. In-hospital mortality and a composite of in-hospital myocardial infarction and cerebrovascular accident according to left main coronary artery involvement and number of diseased vessels.
Adjusted hazard ratio for demographics and in-study outcome predictors is provided for the primary endpoint. LM = left main; HR = hazard ratio, MI/CVA = myocardial infarction/cerebrovascular accident.

calcification (in-hospital mortality 22.0% *vs.* 35.2%, $p < 0.001$, MI/CVA 3.4% *vs.* 4.7% $p < 0.001$, adj-HR 1.35, 95%CI 1.04–1.74, p=0.023) and by the number of calcified vessels (in-hospital mortality one: 21.1% *vs.* two: 25.6% *vs.* three: 33%, $p < 0.001$, MI/CVA one: 2.4% *vs.* two: 3.3% *vs.* three: 5.4%, p=0.137), though non-significant after multivariate adjustment (adj-HR 1.08, 95%CI 0.92–1.26, p=0.355) (Fig. 3).

3.2.3. Sensitivity analysis by age

When stratifying the population according to the median age, increasing rates of in-hospital mortality were observed for patients with no CAD *vs.* subclinical CAD *vs.* clinical CAD in both age subgroups (<70 years: 6.3% *vs.* 14.8% *vs.* 22.9%, $p < 0.001$; ≥70 years: 35.2% *vs.* 36.3% *vs.* 50%). Among patients <70 years, as compared to no CAD, subclinical CAD was associated with an increased risk of in-hospital mortality (adj-HR 2.11 95%CI 1.11–4.01, p=0.023), while numerical trends were observed for clinical CAD (adj-HR 2.83 95%CI 0.92–8.74, p=0.071). In contrast, in patients ≥70 years, subclinical CAD compared to no CAD was not associated with increased risk of in-hospital mortality despite numerical trends (adj-HR 1.44 95%CI 0.86–2.43, p=0.167), while increased risk was observed for patients with clinical CAD (adj-HR 2.19 95%CI 1.16–4.13, p=0.016).

4. Discussion

This study evaluated the impact of clinical and subclinical CAD, as assessed by coronary artery calcium, on in-hospital mortality in a large, unselected population of hospitalized COVID-19 patients undergoing non gated chest CT for pneumonia severity assessment. The main findings were:

1. Clinical and subclinical CAD assessed by CAC score on a routine non-gated chest CT are associated with in-hospital mortality and MI/CVA.
2. This association is independent of comorbidities, clinical, laboratory and lung imaging predictors of COVID-19-related mortality.
3. The extension and location of subclinical coronary artery disease are associated with COVID-19 in-hospital mortality.
4. Clinical cardiovascular risk factors are not independently associated with COVID-19 in-hospital mortality when the extent and presence of coronary atherosclerosis is considered.

Our observations highlight the clinical relevance of the emerging link between SARS-Cov2 infection and the cardiovascular system. Our

results suggest that the atherosclerotic spectrum identifies a vulnerability substratum for COVID-19 disease. The chronic inflammatory state and immune system dysregulation that characterize atherosclerosis may offer an ideal pro-inflammatory milieu for SARS-Cov2 infection. Endothelial cells are one of the targets of the virus and diffuse endothelitis has been described as a mechanism for multiorgan damage in COVID-19 disease. Atherosclerosis is associated with endothelial dysfunction, and together this may confer a higher susceptibility to more aggressive viral replication, inflammatory response and clinical manifestations [13,14]. Of note, both overall in-hospital mortality and MI/CVA events were significantly increased among COVID-19 patients with subclinical and clinical CAD as compared to those without, suggesting a specific interplay of SARS-Cov2 infection with the cardiovascular system. This consideration is supported by the particular thrombotic and clinical features of ST-elevation myocardial infarction among COVID-19 disease, reinforcing the importance of further investigations into developing specific management strategies amongst COVID-19 patients with (subclinical and clinical) CAD disease [15].

On the other hand, given that not all the incremental risk is explained by episode of acute coronary syndrome, one could speculate that CAC is a marker of reduced vascular reserve that penalizes the patients infected with SARS-Cov2.

The fact that clinical and subclinical CAD is associated with an increased risk of long-term mortality and cardiovascular events in the general population is well-known [16]. Our findings extend this concept to the acute setting and short-term prognosis of COVID-19 disease suggesting that a variety of complex mechanisms underlie the link between coronary atherosclerosis and adverse events, beyond acute and chronic coronary syndromes. This link was recently suggested by two small (53 and 209 patients) retrospective single-center experiences which evaluated the impact of subclinical CAD by CAC scoring on outcomes in COVID-19 patients. However, the studies used composite outcomes (death or intensive care unit admission [8], and death or occurrence of mechanical ventilation or extracorporeal membrane oxygenation [9]), with either no [8] or only partial [9] adjustment for important covariates. Our study provides a much broader multi-center experience, testing the hard endpoint of in-hospital mortality, which is less subject to heterogeneity in clinical practice. Furthermore, we provide more granular information on the extension and location of subclinical CAD and adjusted for a broad range of multiparametric covariates taking into account the clinical risk profile and markers of COVID-19 disease severity.

From a clinical standpoint, our results suggest that CAC score may be an objective, readily available tool to complement current COVID-19 disease risk stratification tools [15]. This may be particularly relevant in view of the third wave of the COVID-19 pandemic, which is creating significant demands upon the allocation of human and economic resources in healthcare systems worldwide. Specifically, we observed that the presence and extent of CAC disease is a much better gauge for COVID-19 prognosis as compared to a clinical cardiovascular risk assessment, which is frequently adopted in available COVID-19 prognostication tools [17]. This finding was clinically meaningful as demonstrated by the AUC improvement with "CAD stratification" over the clinical cardiovascular risk profile alone. Interestingly, the finding of additive independent value between the presence and extent of CAD and peripheral artery disease suggests the potential implication of a broader atherosclerotic burden assessment encompassing the whole arterial system. Moreover, CAD severity and extent demonstrated their independent prognostic value against age, peripheral artery disease, active malignancy, elevated lactic dehydrogenase (LDH) level and extent of pneumonia at chest CT which, besides being the independent prognostic predictors in our analysis, represent consistent and robust risk markers across most of the COVID-19 literature. As no significant AUC improvement with "CAD stratification" was observed when the markers of COVID-19 severity were taken into account, this association is rather of pathophysiological relevance and does not seem to justify a more aggressive use of chest CT in COVID-19 with the purpose to quantify CAC, but rather that CAC quantification may provide complementary information when chest CT is performed or available for other clinical reasons, especially in the setting of COVID-19 prevention and pre-emptive risk assessment.

In our cohort more than a third (39.8%) of patients with clinically manifest CAD died during the hospitalization and 12% developed a myocardial infarction or a cerebrovascular accident. Among patients with subclinical CAD, those with a CAC $\geq$400 showed a similar mortality rate (38.7%) to patients with clinical CAD, representing a subset of patients who could have been potentially overlooked by clinical assessment alone. The lower strata of CAC also maintained an additive prognostic value. This suggests that calcium deposition in the coronary artery is a mirror to a more general alteration in the vascular system, independently from overt CAD. Importantly, the subset of patients with zero CAC had a fairly low rate of adverse events (in-hospital mortality 11.3%, MI/CVA 2.3%) pointing at the protective role of a healthy vasculature in the course of COVID-19 disease natural history.

When a qualitative, rather than quantitative approach was applied, by stratifying COVID-19 patients according to the presence of absence of left main coronary artery calcification or number of calcified vessels, a significant association with in-hospital mortality was still observed. This suggests that coronary calcium evaluation either qualitatively or quantitatively on chest CT could potentially be a useful tool to guide physicians performing risk assessments in a busy clinical setting.

4.1. Limitations

This study must be interpreted in the context of some limitations. First, this was a retrospective observational study and outcomes were retrospectively adjudicated at each center without central adjudication. Second, some data regarding important cardiovascular risk factors such as dyslipidemia and CAD family history, along with important metrics of overall frailty status were not collected in the dataset and were thus not considered in the multivariate adjustment, which may have affected the study results [18,19]. Similarly, myocardial injury as defined by peak troponin value, was excluded from the multivariate adjustment because this data was only available for a minority of patients. Third, we only enrolled only COVID-19 patients who were hospitalized and underwent chest CT for lung assessment. Therefore, a selection bias might have occurred as patients with milder disease would not have been represented in the present analysis, although this bias could not be quantified from the data collected in the registry. Moreover, for this reason, most of the exams were not EKG-gated representing suboptimal imaging for quantitative CAC assessment. However, it has been previously demonstrated that CAC assessment based on non-EKG-gated CT is reliable [20] and, more importantly, the results of this analysis suggest its value in the setting of COVID-19 disease prognosis. Fourth, we used the absence of CAC evidence (CAC = 0) as a proxy for no coronary artery disease. Whilst this approach may not fully capture the extent of atherosclerosis from a pathophysiological standpoint, its negative predictive values for clinically and subclinically meaningful CAD approaches 100% and is thus of practical value [21]. To conclude, long-term outcomes of COVID-19 disease were beyond the scope of this investigation.

4.2. Conclusions

The presence and extension of CAD, as assessed by CAC obtained from non-gated chest CT, was associated with higher rates of in-hospital mortality, myocardial infarction and cerebrovascular accident among

hospitalized patients with COVID-19 disease. Furthermore, CAC is a better prognostic marker compared to traditional clinical cardiovascular risk assessment amongst hospitalized COVID-19 patients.

Author contributions

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Declaration of competing interest

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.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2021.03.041.

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