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CLINICAL RESEARCH

Coronary artery calcifications and 6-month mortality in patients with COVID-19 without known atheromatous disease[☆]

Calcifications des artères coronaires et mortalité à 6 mois chez les patients COVID-19 sans maladie athéromateuse connue

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KEYWORDS

COVID-19;
 Coronary artery disease;
 Myocardial injury;
 Risk stratification;
 Mortality

Summary

Background. – Coronary artery calcium (CAC) is an independent risk factor for major adverse cardiovascular events; however, its impact on coronavirus disease 2019 (COVID-19) mortality remains unclear, especially in patients without known atheromatous disease.

Aims. – To evaluate the association between CAC visual score and 6-month mortality in patients without history of atheromatous disease hospitalized with COVID-19 pneumonia.

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin-II receptor blocker; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CI, confidence interval; COVID-19, coronavirus disease 2019; CT, computed tomography; HR, hazard ratio; RAS, renin-angiotensin system; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[☆] Tweet: Coronary artery calcifications and COVID 19..

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Methods. – A single-centre observational cohort study was conducted, involving 293 consecutive patients with COVID-19 in Paris, France, between 13 March and 30 April 2020, with a 6-month follow-up. Patients with a history of ischaemic stroke or coronary or peripheral artery disease were excluded. The primary outcome was all-cause mortality at 6 months according to CAC score, which was assessed by analysing images obtained after the first routine non-electrocardiogram-gated computed tomography scan performed to detect COVID-19 pneumonia.

Results. – A total of 251 patients (mean age 64.8 ± 16.7 years) were included in the analysis. Fifty-one patients (20.3%) died within 6 months. The mortality rate increased with the magnitude of calcifications, and was 10/101 (9.9%), 15/66 (22.7%), 10/34 (29.4%) and 16/50 (32.0%) for the no CAC, mild CAC, moderate CAC and heavy CAC groups, respectively ($p = 0.004$). Compared with the no calcification group, adjusted risk of death increased progressively with CAC: hazard ratio (HR) 2.37 (95% confidence interval [CI] 1.06–5.27), HR 3.1 (95% CI 1.29–7.45) and HR 4.02 (95% CI 1.82–8.88) in the mild, moderate and heavy CAC groups, respectively.

Conclusions. – Non-electrocardiogram-gated computed tomography during the initial pulmonary assessment of patients with COVID-19 without atherosclerotic cardiovascular disease showed a high prevalence of mild, moderate and heavy CAC. CAC score was related to 6-month mortality, independent of conventional cardiovascular risk factors. These results highlight the importance of CAC scoring for patients hospitalized with COVID-19, and calls for attention to patients with high CAC.

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MOTS CLÉS

COVID-19 ;
Coronaropathie ;
Lésion myocardique ;
Stratification du
risque ;
Mortalité

Résumé

Contexte. – La calcification des artères coronaires (CAC) est un facteur de risque indépendant d'événements cardiovasculaires majeurs ; cependant, leur impact sur la mortalité de la maladie à coronavirus 2019 (COVID-19) reste peu clair, en particulier chez les patients sans maladie athéromateuse connue.

Objectifs. – Évaluer l'association entre le score visuel de CAC et la mortalité à 6 mois chez les patients sans antécédents de maladie athéromateuse hospitalisés pour une pneumonie à COVID-19.

Méthodes. – Étude observationnelle monocentrique ayant inclus 293 patients consécutifs hospitalisés pour une pneumonie à COVID-19, entre le 13 mars et le 30 avril 2020. Les patients ayant des antécédents d'accident vasculaire cérébral ischémique, de coronaropathie, ou d'artériopathie oblitérante des membres inférieurs ont été exclus. Le critère de jugement principal était la mortalité toutes causes confondues à 6 mois selon le score visuel de CAC (obtenu en analysant les images du scanner thoracique non synchronisé à l'ECG réalisé à l'admission pour détecter et quantifier l'atteinte pulmonaire au COVID-19).

Résultats. – Au total, 251 patients ($64,8 \pm 16,7$ ans) ont été inclus dans notre analyse. Cinquante et un patients (20,3 %) sont décédés dans les 6 mois. Le taux de mortalité augmentait avec l'ampleur des calcifications et était de 10/101 (9,9 %), 15/66 (22,7 %), 10/34 (29,4 %) et 16/50 (32,0 %) pour les groupes sans CAC, avec CAC léger, modéré et important, respectivement ($p = 0,004$). Par rapport au groupe sans calcification, le risque ajusté de décès augmentait progressivement avec le CAC : HR 2,37 (IC95 % 1,06–5,27), HR 3,1 (IC95 % 1,29–7,45) et HR 4,02 (IC95 % 1,82–8,88) dans les groupes CAC léger, modéré et important, respectivement.

Conclusions. – L'utilisation du scanner thoracique non synchronisé à l'ECG lors de l'évaluation pulmonaire initiale des patients COVID-19 a permis de détecter une forte prévalence de patients présentant des calcifications coronaires à un stade léger, modéré et important. Le score CAC était lié à la mortalité à 6 mois indépendamment des facteurs de risque cardiovasculaire conventionnels. Ces résultats soulignent l'importance de l'intégration du score visuel de CAC pour la stratification du risque chez les patients hospitalisés pour une pneumopathie COVID-19.

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Background

Coronavirus disease 2019 (COVID-19) is caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The outbreak has gradually developed into a pandemic, and has endangered global health. In this health crisis, early risk stratification of severe forms of COVID-19 is essential.

Patients with underlying cardiovascular disease have been identified as being at higher risk of severe forms of COVID-19, which have high mortality rates [1,2]. In contrast, among patients with no previous atherosclerotic cardiovascular disease (ASCVD), risk stratification remains to be clarified.

Atherosclerotic plaque formation can be considered as the intermediary between lifetime exposure to risk factors and clinical events, and can be detected through imaging at a preclinical stage. The amount of coronary artery calcium (CAC), a specific marker of coronary atherosclerosis, correlates with coronary atherosclerotic plaque burden, and appears to reflect the cumulative effects of risk factors and vascular aging [3]. Detection of CAC is considered to play a major role in the primary prevention of coronary artery disease [4], as the existence, extent and progression of CAC has been recognized as an important predictor of cardiovascular events and all-cause mortality in the general population [5,6].

In the management of COVID-19, low-dose chest computed tomography (CT) is regularly performed to confirm the diagnosis, to stage the severity of the disease and to recognize possible complications [7]. As well as evaluation of the lungs, low-dose chest CT allows for a visual assessment of the heart and coronary vessels. The most commonly used grading for clinical quantification of CAC is the Agatston score [8], which requires standardized acquisition and dedicated software to obtain a reliable score.

In an easier way, global visual assessment of the CAC score is achievable on all non-electrocardiogram-gated and non-contrast low-dose CT scans. This visual assessment is an effective, simple and fast method, strongly suggested by several societies for routine reporting, to separate patients into risk categories for either coronary heart disease death or all-cause mortality [9–12]. The question remains whether this visual quantification of CAC can be used to identify, in a patient population without known atheromatous disease, those who are most likely to develop severe forms of COVID-19. Data regarding this specific population are still scarce.

The purpose of this study was to evaluate the association between CAC score assessed by low-dose chest CT in patients without known ASCVD and all-cause mortality within 6 months of hospital admission for COVID-19.

Methods

Patient population

A single-centre observational cohort study was conducted at Georges Pompidou European Hospital, a tertiary teaching hospital in Paris (France). All adult patients (aged ≥ 18 years) who required hospitalization for at least 48 hours between

13 March and 30 April 2020 for COVID-19, confirmed by reverse transcription-polymerase chain reaction, and with a chest CT scan at admission were eligible. Patients with a history of ischaemic stroke, coronary artery disease or peripheral artery disease (i.e. ASCVD) were excluded.

This study is part of the French COVID cohort study (a prospective cohort study conducted to determine COVID-19 physiopathology; ClinicalTrials.gov identifier: NCT04262921). All patients provided written informed consent before enrolment, and were informed that their medical data could be used for research purposes in accordance with the General Data Protection Regulation (EU 2016/679).

Data collection

Data were collected from the centre's electronic medical records, and included patient demographic characteristics (age and sex), cardiovascular risk factors, past medical history, presenting vital signs and symptoms, laboratory findings, treatment before admission, complications and outcomes. Cardiovascular risks factors were defined using international recommendations, and obesity was defined as body mass index $> 30 \text{ kg/m}^2$ [13]. From the medical history collected, we grouped both active cancers and those in remission in the cancer category. Participants were followed up by telephone by local trial personnel at the end of October 2020, after at least a 6-month period for all patients.

CT scan

All low-dose chest CT scans were performed on the same multi-row system (Somatom Definition Edge, Siemens, Munich, Germany), and were obtained from the lung apices to the bases in a single breath hold at maximum inspiration without electrocardiogram gating [14]. Each of the five lung lobes was assessed for the presence (counting for 1 point) or absence (counting for 0 points) of COVID-19 damage, defined by either ground-glass opacities or consolidation or both. By adding the visual scores of the five lobes per patient, the total severity score was estimated over a range from 0 to 5.

As described in our previous study [15], quantification of CAC was performed using standard mediastinal parameters (width, 350 Hounsfield units; level, 50 Hounsfield units), and according to the guidelines for CAC scoring of non-contrast non-cardiac chest CT scans [10].

Calcium scoring was performed independently of care by two radiologists with expertise in cardiothoracic imaging, who were blinded from all clinical data, biology and initial chest CT analysis. After a visual CAC assessment, the radiologists provided a score in four categories: none, mild, moderate and heavy CAC. The detailed method is described in the Appendix.

Biological data and cardioprotective treatments

For each patient, a biological workup, including complete blood count, ionogram, creatinine, C-reactive protein, brain natriuretic peptide and troponin, was collected at

admission. The high-sensitivity troponin I value at admission and the peak value were recorded.

Myocardial injury was defined by elevated cardiac troponin concentrations above the 99th percentile upper reference limit. Myocardial infarction was defined as a significant modification of the electrocardiogram, associated with an elevation of troponin I value or typical chest pain. Cardioprotective treatments assessed in this study were antiplatelet therapies (aspirin 75 mg or 100 mg or clopidogrel 75 mg per day), statins, renin-angiotensin system (RAS) blockers (including angiotensin-converting enzyme inhibitors [ACE inhibitors] and angiotensin-II receptor blockers [ARBs]) and beta-blockers used for chronic heart failure (carvedilol, metoprolol, bisoprolol and nebivolol).

We categorized patients into three groups according to their initial medication: those naive of any cardioprotective treatment, those taking only one drug and those taking two or more drugs. Patients taking a combination of treatments in a single galenic form (e.g. a combination of an ACE inhibitor and beta-blocker in one pill) were counted as taking two cardioprotective treatments.

Outcomes

The primary outcome was all-cause mortality, including in- and out-of-hospital deaths, within 6 months following hospital admission, according to CAC scoring.

Secondary outcomes included 6-month mortality according to myocardial injury (defined by elevated cardiac troponin concentrations above the 99th percentile upper reference limit), and according to number of cardioprotective treatments used before admission, to determine whether these therapies might have a beneficial role in preventing mortality in patients with COVID-19.

Statistical analysis

Groups were compared by analysis of variance for continuous variables and χ^2 tests for categorical variables. Hazard ratios (HRs) are presented with their 95% confidence intervals (CI). Survival curves were estimated using Kaplan-Meier estimators, and were compared according to CAC scores using log-rank tests. The rates of all-cause mortality at 6 months were analysed according to CAC scores, and the impact of CAC was evaluated using a multivariable backward stepwise Cox analysis, with a threshold of 0.20 for variable elimination. Variables included in the models were selected *ad hoc*, based on their physiological relevance. Four analyses were performed: (1) CAC categories and pulmonary extent of COVID-19 pneumonia; (2) model 1 + age, sex, cardiovascular risk factors (hypertension, dyslipidaemia, diabetes, obesity), cancer; (3) model 2 + myocardial injury; and (4) model 3 + cardiopreventive treatments. All analyses were repeated using forward stepwise analysis to check the consistency of the results. Collinearity was tested by calculation of variance inflation factors. Statistical analyses were performed using IBM SPSS 26.0 (IBM SPSS Inc., Chicago, IL, USA). For all analyses, two-sided *P* values < 0.05 were considered significant.

Results

Patient characteristics

Of the 293 patients hospitalized for COVID-19 during the 1.5-month recruitment period, 251 with available medical information and thoracic CT scans were included in the present analysis. Baseline characteristics are presented in Table 1. The mean age was 64.8 ± 16.7 years, 165 (65.7%) patients were male, and the mean body mass index was 26.5 ± 5.1 kg/m². Hypertension (40.6%), dyslipidaemia (22.3%), diabetes (18.7%) and obesity (18.1%) were the most common risk factors. There were 46 patients (18.3%) with a history of cancer, 23 (9.2%) with chronic renal disease, 15 (6.0%) with atrial fibrillation and 11 (4.4%) with history of venous thromboembolism. The proportions of no, mild, moderate and heavy CAC were 40.2% (101/251), 26.3% (66/251), 13.5% (34/251) and 19.9% (50/251), respectively. Degree of CAC increased with age and risk factors. Patients with heavy CAC had more co-morbidities, such as dyslipidaemia, hypertension and cancer, compared with other categories.

A total of 109 patients (43.4%) were receiving at least one cardioprotective treatment before admission: 38 (15.1%) were being treated with a statin, 25 (10.0%) with aspirin, 62 (24.7%) with a RAS blocker (ACE inhibitor or ARB) and 40 (15.9%) with a beta-blocker. Among the 43 patients receiving two or more treatments, RAS blockers were prescribed in a large majority (72.1%), followed by statins (62.8%), beta-blockers (51.2%) and aspirin (44.2%). Those who received two or more treatments were older (59.9 vs. 72 years; $P < 0.0001$) and had more co-morbidities, such as dyslipidaemia (67.4% vs. 6.3%; $P < 0.0001$), diabetes (37.2% vs. 13.4%; $P = 0.002$), hypertension (86.1% vs. 15.5%; $P < 0.0001$), atrial fibrillation (4.7% vs. 0.7%; $P < 0.0001$) and chronic renal insufficiency (23.3% vs. 1.4%; $P < 0.0001$). Finally, statins, aspirin, RAS blockers and beta-blockers were more prescribed before hospitalization in patients with heavy CAC than in patients without CAC.

Laboratory and CT findings

Laboratory findings are presented in Table 1; they were balanced between categories, except for cardiac biomarkers (i.e. brain natriuretic peptide and troponin concentration), which increased as the CAC burden grew.

Myocardial injury affected 116 patients (46.2%) in our study and increased progressively according to CAC score ($P < 0.001$) (Table 2, Fig. 1). In this group, the mean age was significantly higher than in the non-myocardial injury group (70.8 vs. 59.7 years; $P < 0.0001$). Patients with myocardial injury had significantly more co-morbidities, such as hypertension (50.9% vs. 33.8%), atrial fibrillation (9.5% vs. 3.0%) and chronic renal disease (14.7% vs. 4.4%), than the non-myocardial injury group. As a result, the number of prescriptions for curative anticoagulation, RAS blockers, ACE inhibitors, ARBs, beta-blockers, calcium channel blockers and diuretics was higher in the myocardial injury group.

Thoracic CTs were performed during the first 24 hours after admission in 90% of patients. The proportion of patients with bilateral pneumonia was 62.5% (157 patients), and the proportion with at least three lung lobes affected

Table 1 Baseline characteristics, laboratory and radiographic findings.

	CAC score				Overall population (n = 251)	P
	None (n = 101)	Mild (n = 66)	Moderate (n = 34)	Heavy (n = 50)		
Age (years)	53.0 ± 14.7	69.6 ± 12.8	72.7 ± 12.0	77.4 ± 12.0	64.8 ± 16.7	< 0.0001
Men	73 (72.3)	41 (62.1)	20 (58.8)	31 (62.0)	165 (65.7)	0.34
Body mass index (kg/m ²)	27.3 ± 5.6	26.3 ± 4.3	26.3 ± 6.4	25.1 ± 3.6	26.5 ± 5.1	0.26
Body mass index > 30 kg/m ²	21 (22.1) (n = 95)	11 (17.7) (n = 62)	6 (18.7) (n = 32)	4 (9.3) (n = 43)	42 (18.1) (n = 232)	0.30
Admission to intensive care unit	32 (31.7)	27 (40.9)	9 (26.5)	9 (18.0)	77 (30.7)	0.06
Cardiovascular risk factors						
Dyslipidaemia	10 (9.9)	16 (24.2)	14 (41.2)	16 (32.0)	56 (22.3)	0.0003
Diabetes	11 (10.9)	15 (22.7)	9 (26.5)	12 (24.0)	47 (18.7)	0.07
Hypertension	22 (21.8)	32 (48.5)	19 (55.9)	29 (58.0)	102 (40.6)	< 0.0001
Smoker or ex-smoker	19 (18.8)	17 (25.8)	10 (29.4)	21 (42.0)	67 (26.7)	0.02
Medical history						
Atrial fibrillation	3 (3.0)	3 (4.5)	3 (8.8)	6 (12.0)	15 (6.0)	0.16
Rhythm disorders	3 (3.0)	5 (7.6)	1 (2.9)	0 (0.0)	9 (3.6)	0.10
Non-significant valvular disease	3 (3.0)	4 (6.1)	1 (2.9)	0 (0.0)	8 (3.2)	0.19
VTE disease	2 (2.0)	3 (4.5)	1 (2.9)	5 (10.0)	11 (4.4)	0.19
Chronic renal disease	6 (5.9)	6 (9.1)	5 (14.7)	6 (12.0)	23 (9.2)	0.55
Pacemaker	0 (0.0)	1 (1.5)	2 (5.9)	3 (6.0)	6 (2.4)	0.04
ICD	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.0)	2 (0.8)	0.21
Asthma	9 (8.9)	6 (9.1)	2 (5.9)	3 (6.0)	20 (8.0)	0.86
COPD	4 (4.0)	4 (6.1)	4 (11.8)	3 (6.0)	15 (6.0)	0.49
Cancer	14 (13.9)	10 (15.1)	6 (17.6)	16 (32.0)	46 (18.3)	0.04
Previous medication						
Statins	8 (7.9)	10 (15.2)	10 (29.4)	10 (20.0)	38 (15.1)	0.02
Aspirin	3 (3.0)	7 (10.6)	7 (20.6)	8 (16.0)	25 (10.0)	0.006
Curative anticoagulation	5 (4.9)	8 (12.1)	2 (5.9)	7 (14.0)	22 (8.8)	0.18
RAS blockers	11 (10.9)	20 (30.3)	13 (38.2)	18 (36.0)	62 (24.7)	0.0004
ACE inhibitors	3 (3.0)	7 (10.6)	2 (5.9)	5 (10.0)	17 (6.8)	0.18
ARBs	8 (7.9)	14 (21.2)	11 (32.4)	13 (26.0)	46 (18.3)	0.003
Beta-blockers	10 (9.9)	10 (15.1)	6 (17.6)	14 (28.0)	40 (15.9)	0.04
Use of cardioprotective treatment	23 (22.8)	31 (47.0)	24 (70.6)	31 (62.0)	109 (43.4)	< 0.0001
Calcium channel blockers	13 (12.9)	13 (19.7)	4 (11.8)	11 (22.0)	41 (16.4)	0.37
MRAs	1 (1.0)	2 (3.0)	3 (8.8)	5 (10.0)	11 (4.4)	0.04
Diuretics	6 (5.9)	11 (16.7)	8 (23.5)	11 (22.0)	36 (14.4)	0.009

Table 1 (Continued)

	CAC score				Overall population (n = 251)	P
	None (n = 101)	Mild (n = 66)	Moderate (n = 34)	Heavy (n = 50)		
Clinical presentation						
Dyspnoea	79 (78.2)	44 (66.7)	24 (70.6)	31 (62.0)	178 (70.9)	0.16
Chest pain	14 (13.9)	6 (9.1)	1 (2.9)	6 (12.0)	27 (10.8)	0.24
Diarrhoea	25 (24.7)	17 (25.8)	8 (23.5)	9 (18.0)	59 (23.5)	0.77
Cough	60 (59.4)	40 (60.6)	20 (58.8)	26 (52.0)	146 (58.2)	0.80
Temperature (°C)	37.9 ± 0.96	37.8 ± 0.99	37.9 ± 0.88	37.6 ± 0.91	37.9 ± 0.96	0.16
Heart rate (beats/min)	98 ± 17.6	89 ± 17.2	88 ± 19.3	86.5 ± 17.7	92.7 ± 18.1	0.005
Systolic blood pressure (mmHg)	131.0 ± 17.2	131.5 ± 23.1	132.5 ± 18.8	129.0 ± 26.4	131.9 ± 21.0	0.98
SO ₂ (a) (%)	92.8 ± 7.7	91.6 ± 6.0	92.4 ± 7.2	92.2 ± 6.6	92.3 ± 7.0	0.37
Laboratory findings						
Creatinine (μmol/L)	74 (61.5–90)	82 (65–101)	79 (61–110.5)	84.5 (66–130)	79 (64–104)	0.18
CRP (mg/L)	96 (34–171) (n = 98)	94 (54–131) (n = 66)	103 (37.5–136) (n = 34)	98 (50–159) (n = 50)	97 (46–155) (n = 248)	0.99
Haemoglobin (g/dL)	13.9 (12.8–14.9)	13.4 (12.1–14.5)	13.5 (12.4–14.6)	12.9 (11.4–14.5)	13.7 (12.2–14.7)	0.03
Neutrophils (×10 ⁶ /L)	4970 (3020–6580)	5185 (3460–7715)	4850 (3127–6532)	5000 (3770–7535)	5010 (3422–7100)	0.56
Lymphocytes (×10 ⁶ /L)	990 (740–1345)	995 (620–1275)	780 (517–1152)	750 (485–1315)	950 (620–1290)	0.69
Platelets (×10 ⁹ /L)	204 (160–243)	196 (152–257.5)	182 (141–242.5)	207 (145–287)	197.5 (153–255)	0.56
hs-Troponin I (ng/L)	7.9 (4.3–15.3) (n = 97)	13.7 (5.5–29.4) (n = 64)	13.7 (7.2–31.1) (n = 33)	18.6 (10.0–33.9) (n = 48)	11.8 (5.5–22.9) (n = 242)	< 0.001
hs-Troponin I peak (ng/L)	11.3 (4.3–28.2) (n = 97)	24 (7.4–94.6) (n = 64)	25.6 (7.7–67.6) (n = 33)	22.5 (13.3–64.5) (n = 48)	8.2 (7.0–57.0) (n = 242)	< 0.0001
Myocardial injury	35 (34.6)	35 (53.0)	17 (50.0)	29 (58.0)	116 (46.2)	0.02
BNP (ng/L)	21 (13.0–53.5) (n = 77)	48 (18.5–164) (n = 53)	40 (19–160) (n = 29)	91.5 (48.5–246.2) (n = 44)	46 (19–126) (n = 203)	< 0.0001
Outcomes						
Death at 6 months	10 (9.9)	15 (22.7)	10 (29.4)	16 (32.0)	51 (20.3)	0.004
HF during hospitalization	3 (3.0)	8 (12.1)	1 (2.9)	2 (4.0)	14 (5.6)	0.09
Rhythm disorders during hospitalization	6 (5.9)	11 (16.7)	3 (8.8)	6 (12.0)	26 (10.4)	0.16
Lung damage score on chest CT > 4	78 (77.2)	53 (80.3)	30 (88.2)	34 (68.0)	195 (77.7)	0.15

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; BNP: brain natriuretic peptide; CAC: coronary artery calcium; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; CT: computed tomography; HF: heart failure; hs-Troponin I: high-sensitivity troponin I; ICD: implantable cardioverter-defibrillator; MRA: mineralocorticoid receptor antagonist; RAS: renin-angiotensin system; SO₂(a): arterial oxygen saturation; VTE: venous thromboembolism.

Table 2 Clinical characteristics according to myocardial injury.

	No myocardial injury (n = 135)	Myocardial injury (n = 116)	Overall population (n = 251)	P
Age (years)	59.7 ± 16.2	70.8 ± 15.2	64.8 ± 16.7	< 0.0001
Men	89 (65.9)	76 (65.5)	165 (65.7)	0.94
Body mass index (kg/m ²)	26.2 ± 4.8	26.8 ± 5.3	26.5 ± 5.1	0.51
Admission to intensive care unit	21 (15.6)	56 (48.3)	77 (30.7)	< 0.0001
Cardiovascular risk factors				
Dyslipidaemia	27 (20.0)	29 (25.0)	56 (22.3)	0.34
Diabetes	24 (17.8)	23 (19.8)	47 (18.7)	0.68
Hypertension	43 (33.8)	59 (50.9)	102 (40.6)	0.002
Medical history				
Atrial fibrillation	4 (3.0)	11 (9.5)	15 (6.0)	0.03
Rhythm disorder	4 (3.0)	5 (4.3)	9 (3.6)	0.57
Valvular disease	2 (1.5)	6 (5.2)	8 (3.2)	0.15
VTE disease	5 (3.7)	6 (5.2)	11 (4.4)	0.57
Chronic renal disease	6 (4.4)	17 (14.7)	23 (9.2)	0.02
Pacemaker	0 (0.0)	6 (5.2)	6 (2.4)	0.002
ICD	0 (0.0)	2 (1.7)	2 (0.8)	0.21
Asthma	13 (9.6)	7 (6.0)	20 (8.0)	0.35
COPD	6 (4.4)	9 (7.7)	15 (6.0)	0.27
Cancer (any type)	19 (14.1)	27 (23.3)	46 (18.3)	0.06
Previous medication				
Statins	19 (14.1)	19 (16.4)	38 (15.1)	0.61
Aspirin	13 (9.6)	12 (10.3)	25 (10.0)	0.85
Curative anticoagulation	7 (5.2)	15 (12.9)	22 (8.8)	0.03
RAS blockers	21 (15.6)	41 (35.4)	62 (24.7)	0.0003
ACE inhibitors	4 (3.0)	13 (11.2)	17 (6.8)	0.01
ARBs	17 (12.6)	29 (25.0)	46 (18.3)	0.01
Beta-blockers	15 (11.1)	25 (21.5)	40 (15.9)	0.02
Use of cardioprotective treatment (listed above)	49 (36.3)	60 (51.7)	109 (43.4)	0.01
Calcium channel blockers	15 (11.1)	26 (22.4)	41 (16.3)	0.01
MRAs	4 (3.0)	7 (6.0)	11 (4.4)	0.35
Diuretics	13 (9.6)	23 (19.8)	36 (14.3)	0.02
Clinical presentation				
Dyspnoea	96 (71.1)	82 (70.7)	178 (70.9)	0.94
Chest pain	19 (14.1)	8 (6.9)	27 (10.8)	0.06
Diarrhoea	37 (27.4)	22 (19.0)	59 (23.5)	0.11
Cough	88 (65.2)	58 (50.0)	146 (58.2)	0.01
Temperature (°C)	37.9 ± 0.8	37.9 ± 1.1	37.9 ± 0.96	0.90
Heart rate (beats/min)	94.5 ± 14.3	90.7 ± 21.6	92.7 ± 18.1	0.03
Systolic blood pressure (mmHg)	131.4 ± 19.2	132.4 ± 23.0	131.9 ± 21.0	0.71
SO ₂ (a) (%)	93.6 ± 4.7	90.8 ± 8.7	92.3 ± 7.0	0.005
Biology findings				
Creatinine (μmol/L)	71 (61–86)	94 (72–127)	79 (64–104)	< 0.0001
CRP (mg/L)	73 (36–119)	125 (59–202)	97 (46–155)	< 0.0001
Haemoglobin (g/dL)	13.9 (12.7–15.0)	13.2 (12.1–14.3)	13.7 (12.2–14.7)	0.008
Neutrophils (×10 ⁶ /L)	4320 (3100–6060)	5820 (3930–8280)	5010 (3422–7100)	< 0.0001
Lymphocytes (×10 ⁶ /L)	990 (750–1300)	840 (520–1260)	950 (620–1290)	0.03
Platelets (×10 ⁹ /L)	204.5 (158–257)	184.5 (144–252)	197.5 (153–255)	0.16
Outcomes				
Death at 6 months	8 (5.9)	43 (37.1)	51 (20.3)	< 0.0001
HF during hospitalization	1 (0.7)	13 (11.2)	14 (5.6)	0.0004
Rhythm disorders during hospitalization	2 (1.4)	24 (20.7)	26 (10.4)	< 0.0001

Table 2 (Continued)

	No myocardial injury (n = 135)	Myocardial injury (n = 116)	Overall population (n = 251)	P
Lung damage score on chest CT > 4	96 (71.1)	99 (85.3)	195 (77.7)	0.007
CAC score				0.02
None	66 (48.9)	35 (30.2)	101 (40.2)	
Mild	31 (23.0)	35 (30.2)	66 (26.3)	
Moderate	17 (12.6)	17 (14.7)	34 (13.5)	
Heavy	21 (15.6)	29 (25.0)	50 (19.9)	

Data are expressed as mean ± standard deviation, number (%) or median (interquartile range). ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CAC: coronary artery calcium; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; CT: computed tomography; HF: heart failure; ICD: implantable cardioverter-defibrillator; MRA: mineralocorticoid receptor antagonist; RAS: renin-angiotensin system; SO₂(a): arterial oxygen saturation; VTE: venous thromboembolism.

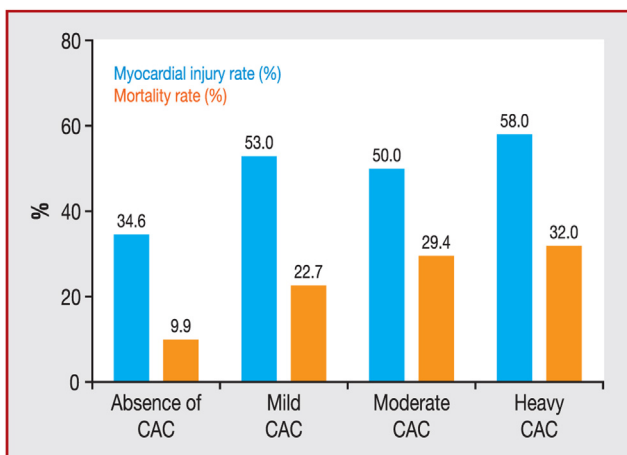


Figure 1. Association between myocardial injury, mortality rate and coronary artery calcium (CAC) score ($P < 0.001$).

by consolidation was 70.5% (177 patients). No difference was observed between CAC categories.

Coronary calcifications and mortality

During the 6-month follow-up, a total of 51 patients (20.3%) died. The mortality rate increased with the extent of CAC: in the group without CAC, 10 patients out of 101 died (9.9%), whereas in the groups with mild, moderate and heavy CAC, there were 15 deaths out of 66 patients (22.7%), 10 deaths out of 34 (29.4%) and 16 deaths out of 50 (32.0%), respectively ($P = 0.004$) (Fig. 1). Table A.1 compares the characteristics of patients according to their vital status at 6 months.

In the multivariable analysis, CAC was associated with all-cause mortality at 6 months, with an HR of 2.37 (95% CI 1.06–5.27) for mild CAC, 3.1 for moderate CAC (95% CI 1.29–7.45) and 4.02 for heavy CAC (95% CI 1.82–8.88) compared with patients with no CAC (Table 3; Fig. 2). In this model, pulmonary extent of COVID-19 pneumonia was also associated with higher mortality (HR 2.5, 95% CI 1.06–5.91).

Consistent trends were found using several sensitivity analyses: CAC was still associated with 6-month mortality after adjustment for cardiovascular risk factors, myocardial injury and cardioprotective treatments (Table 3). After

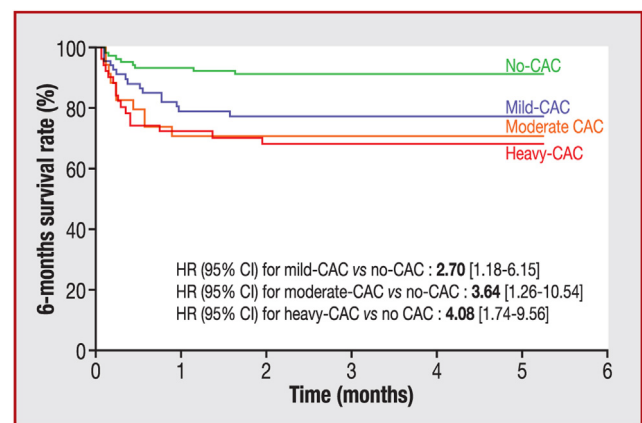


Figure 2. Kaplan-Meier survival curves for mortality according to category of coronary artery calcium (CAC). CI: confidence interval; HR: hazard ratio.

excluding patients with atrial fibrillation ($n = 9$), valvular disease ($n = 8$) and previous venous thromboembolism disease ($n = 11$), we found similar results for the primary outcome (data not shown).

Myocardial injury, use of cardioprotective treatment and mortality

In the myocardial injury group, hospitalizations were complicated with episodes of heart failure for 13 patients (11.2%), compared with one patient (0.7%) in the non-myocardial injury group ($P = 0.0004$), and 24 patients (10.4%) had rhythm disorders, compared with two patients (1.4%) in the non-myocardial injury group ($P < 0.0001$) (Table 2).

When troponin was elevated, mortality was significantly higher. Indeed, we reported 43 deaths (37.1%) in the myocardial injury group compared with only eight deaths (5.9%) in the non-myocardial injury group ($P < 0.0001$). Deaths occurred early in most cases, before the 30th day (Fig. A.1). In a multivariable analysis with a Cox proportional hazards model of mortality, myocardial injury was an independent predictor of mortality (HR 5.73, 95% CI 2.63–12.48) (Table 3).

Using non-adjusted analysis, we found no difference in mortality between groups according to their use of

Table 3 Multivariable Cox regression analysis on mortality at 6 months.

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age	—	—	1.03 (0.99–1.04)	0.10	1.003 (0.98–1.03)	0.83	1.00 (0.97–1.03)	0.99
Male sex	—	—	0.94 (0.52–1.09)	0.83	1.19 (0.65–2.16)	0.57	1.15 (0.63–2.10)	0.65
Pulmonary extent of COVID-19 pneumonia	2.5 (1.06–5.91)	0.04	3.30 (1.26–8.52)	0.01	3.44 (1.27–9.31)	0.015	3.61 (1.33–9.77)	0.01
Coronary artery calcium								
None (ref.)	—	—	—	—	—	—	—	—
Mild	2.37 (1.06–5.27)	0.04	1.76 (0.73–4.21)	0.21	1.59 (0.67–3.74)	0.29	1.91 (0.81–4.49)	0.14
Moderate	3.10 (1.29–7.45)	0.01	2.16 (0.83–5.63)	0.11	3.48 (1.39–8.72)	0.008	3.93 (1.55–10.0)	0.004
Heavy	4.02 (1.82–8.88)	0.001	2.52 (0.97–6.54)	0.06	3.74 (1.53–9.16)	0.004	4.05 (1.62–10.13)	0.003
Diabetes	—	—	1.03 (1.001–1.05)	0.04	0.49 (0.22–1.08)	0.08	—	—
History of cancer	—	—	2.86 (1.49–5.48)	0.002	3.44 (1.79–6.60)	< 0.001	3.15 (1.64–6.06)	0.001
Body mass index > 30 kg/m ²	—	—	2.03 (0.98–4.19)	0.06	2.03 (0.96–4.31)	0.06	—	—
Myocardial injury	—	—	—	—	5.73 (2.63–12.48)	< 0.001	6.0 (2.78–13.0)	< 0.001
Cardiopreventive treatment	—	—	—	—	—	—	0.67 (0.46–0.97)	0.03

CI: confidence interval; COVID-19: coronavirus disease 2019; HR: hazard ratio. Model 1: adjusted on coronary artery calcium categories and pulmonary extent of COVID-19 pneumonia. Model 2: Adjusted on Model 1 + age, sex, cardiovascular risk factors (hypertension, dyslipidaemia, diabetes, obesity) and cancer. Model 3: Adjusted on Model 2 + myocardial injury. Model 4: Adjusted on Model 3 + cardiopreventive treatment.

cardioprotective treatments: 10 deaths occurred in the group using two or more treatments (23.3%), 14 in the group using one treatment (21.2%) and 27 in the no-treatment group (19%) ($P=0.81$) (Fig. A.2). Results were consistent concerning complications during hospitalization ($P=0.52$ for number of heart failure episodes; $P=0.25$ for rhythm disorders). Interestingly, in a multivariable Cox regression analysis of mortality, undergoing one or more cardioprotective therapies was an independent protective factor (HR 0.67, 95% CI 0.46–0.97) (Table 3).

Discussion

Previously, using the same methodology, we showed that the CAC visual score obtained on non-gated thoracic CT scans in all patients with COVID-19 pneumonia (i.e. primary and secondary prevention) was an independent predictor of 6-month mortality. The objective of the present analysis was to demonstrate this association in patients without ASCVD, to define high-risk patients in this population according to CAC score [15].

The main finding of our study is that the CAC visual score seems to be an independent predictor of 6-month mortality in patients hospitalized for COVID-19 without known ASCVD. Patients with higher CAC burden had a higher risk of death, regardless of the extent of lung damage, cardiovascular risk factors, the presence of myocardial injury and the use of cardioprotective treatments. This finding is consistent with the results of two studies published in 2021 that explored the influence of CAC on the prognosis of COVID-19 in this specific population without known coronary artery disease. The first was a multicentre retrospective cohort study involving 2067 patients; it reported that high CAC was a risk factor associated with in-hospital death and adverse clinical outcomes in patients with confirmed COVID-19 [16]. In the second study, the researchers performed a visual assessment of CAC in 280 patients, and found that the absence of CAC had a high negative predictive value for major adverse cardiovascular events in patients during their hospitalization for COVID-19 [17].

Furthermore, in our study, myocardial injury was present in 46.2% of patients, and was associated with unfavourable outcomes, such as admission to intensive care, episodes of heart failure and rhythm disorders during hospitalization and a significantly higher rate of all-cause mortality, which is consistent with several recent studies that found that myocardial injury caused by COVID-19 is associated with poor prognosis [18–26].

Importantly, in the present study, we found an interplay between CAC categories, myocardial injury at admission or during hospitalization and mortality: patients with heavy CAC had significantly greater myocardial injury ($P=0.02$). This finding is supported by a retrospective study including 332 patients hospitalized with COVID-19 with a median follow-up of 12 days, which reported that patients with myocardial injury had a lower prevalence of a CAC score of zero (25%) compared with patients without myocardial injury (55%) ($P<0.001$) [27]. Future studies are needed to elucidate the underlying mechanism that links CAC to myocardial injury and mortality.

All of these findings suggest a close relationship between COVID-19 and the cardiovascular system. To date, the literature has reported conflicting results concerning the use of cardioprotective treatments in COVID-19 [28]. In our study, these treatments did not provide any benefit in terms of mortality at 6 months, probably because of the small size of our population. However, including a treatment such as statins, antiplatelet therapy, beta-blockers and/or RAS blockers as a preventive measure in case of moderate or heavy CAC burden, independent of conventional risk factors, may be beneficial. Such a strategy is supported by the results of recent retrospective studies, in which the anti-inflammatory effect of statins and aspirin has been put forward to explain the decrease in mortality from COVID-19 [29–31]. With regards to RAS inhibitors, the use of ACE inhibitors and ARBs became controversial at the beginning of the pandemic, as they were thought to worsen the patient's condition. Indeed, animal studies have reported that these treatments upregulate the expression of angiotensin-converting enzyme receptor 2, which is also the receptor used by SARS-CoV-2 to infect human cells [32–34]. International scientific societies now recommend continuation of these treatments, however, after several observational studies demonstrated no association between the use of RAS inhibitors and the risk or severity of infection with SARS-CoV-2 [33,35–41]. These data were confirmed by the BRACE CORONA trial, the first randomized cohort study evaluating the clinical impact of discontinuing or continuing ACE inhibitors or ARBs in COVID-19. For the 659 patients involved, no significant difference was found in the number of days of out-of-hospital survival at 30 days between stopping or continuing ACE inhibitors/ARBs in patients hospitalized with COVID-19 [42], suggesting that these treatments should be continued during hospitalization, at least in mild and moderate forms of COVID-19.

Large randomized controlled trials are needed to better understand the association between cardioprotective therapies and survival of COVID-19.

Study limitations

This study has some limitations. First, there is a selection bias because the most severe patients were admitted directly to the intensive care unit, without having a chest CT scan; these patients were therefore not included in our analysis. However, we selected all adult patients hospitalized for more than 2 days; so, in effect, we eliminated all the minor and/or asymptomatic cases who did not need oxygen support. Second, our study was conducted during the first pandemic wave, when there was neither specific treatments (such as corticoids or anti-interleukin-6 receptors) nor vaccines; this may explain our high mortality rate. Our results are therefore not generalizable to a vaccinated population. Third, we included in the "cancer" group both patients in remission and those with active cancer, which introduces a bias that influences the mortality rate. Fourth, the size of our population is quite modest, and so the extrapolation of these results is limited. Fifth, the numbers of variables included in models 2–4 are high regarding the number of events for the primary outcome. These results can only be considered hypothesis generating, and future randomized studies are needed to confirm these data. Finally, given the

observational nature of this work and the use of electronic medical records, the possibility exists of residual confounding.

Conclusions

In conclusion, in patients hospitalized for COVID-19 without known ASCVD, the CAC visual scores obtained from non-gated thoracic CTs seem to be an independent predictor of 6-month all-cause mortality, and could be used systematically in the initial evaluation of hospitalized patients when a chest CT is performed. The detection of CAC and cardiac troponin testing during hospitalization are simple ways to screen patients most at risk. Given the complex influence of COVID-19 on the cardiovascular system, further investigation into potential mechanisms is needed to guide effective therapies. Larger and randomized trials are needed to investigate treatment modalities to reduce the incidence and mortality associated with COVID-19.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.acvd.2022.02.007>.

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