Impact of the “atherosclerotic pabulum” on in-hospital mortality for SARS-CoV-2 infection. Is calcium score able to identify at-risk patients?

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Abstract

Background: Although the primary cause of death in COVID-19 infection is respiratory failure, there is evidence that cardiac manifestations may contribute to overall mortality and can even be the primary cause of death. More importantly, it is recognized that COVID-19 is associated with a high incidence of thrombotic complications.

Hypothesis: Evaluate if the coronary artery calcium (CAC) score was useful to predict in-hospital (in-H) mortality in patients with COVID-19. Secondary end-points were needed for mechanical ventilation and intensive care unit admission.

Methods: Two-hundred eighty-four patients (63, 25 years, 67% male) with proven severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection who had a noncontrast chest computed tomography were analyzed for CAC score. Clinical and radiological data were retrieved.

Results: Patients with CAC had a higher inflammatory burden at admission (d-dimer, $p = .002$; C-reactive protein, $p = .002$; procalcitonin, $p = .016$) and a higher high-sensitive cardiac troponin I (HScTnI, $p = <.001$) at admission and at peak. While there was no association with presence of lung consolidation and ground-glass opacities, patients with CAC had higher incidence of bilateral infiltration ($p = .043$) and higher in-H mortality ($p = .048$). On the other side, peak HScTnI $>$200 ng/dl was a better determinant of all outcomes in both univariate ($p = <.001$) and multivariate analysis ($p = <.001$).
**Conclusion:** The main finding of our research is that CAC was positively related to in-H mortality, but it did not completely identify all the population at risk of events in the setting of COVID-19 patients. This raises the possibility that other factors, including the presence of soft, unstable plaques, may have a role in adverse outcomes in SARS-CoV-2 infection.

**KEYWORDS**
cardiovascular risk, chest computed tomography, coronary calcium score, SARS-CoV-2 infection

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**1 | INTRODUCTION**

Since December 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected more than 118 million people worldwide and it was declared a pandemic by World Health Organization on March 11, 2020.

Although the primary cause of death in COVID-19 infection is respiratory failure, there are evidence that cardiac manifestations may contribute to overall mortality and can even be the primary cause of death. More importantly, it is recognized that COVID-19 is associated with a high incidence of thrombotic complications and that the thrombotic diathesis is due to endothelial cell dysfunction. Of note, while there is a strong evidence that known risk factors for coronary artery disease (CAD), such as age, hypertension, and diabetes, are associated with a poorer prognosis, it has been shown that patients with reduced ventricular function do not have increased mortality compared to controls. In this context, the coronary artery calcium score (CAC score), an established and validated prognostic indicator of CAD, has been of utmost importance in recognizing patients at high risk of poor outcome. Indeed, there are increasing evidence that plaque characteristics are important in defining accurate cardiovascular risk beyond calciﬁcations. Therefore, our hypothesis was to verify if CAC per se is able to identify patients at risk of adverse outcomes and in-hospital (in-H) death in patients with SARS-CoV-2.

**2 | METHODS**

**2.1 | Study population**

We conducted a retrospective, post hoc analysis of all patients admitted to Padua University Hospital with a confirmed COVID-19 diagnosis by polymerase chain reaction (PCR) from January 2020 to January 2021. Sample for real-time PCR was obtained by nasal–oral pharyngeal swab. Exclusion criteria were a history of previous percutaneous coronary artery stenting or coronary bypass surgery, as it may interfere with CAC score calculation. We included patients with known previous CAD who were under medical treatment.

Our population consisted of 284 patients who underwent chest computed tomography (CT) scans because of moderate or severe COVID-19 infection, according to World Health Organization guidelines. Baseline demographic, clinical, and laboratory variables (including inflammatory biomarkers) were retrieved from our electronic medical record system. High-sensitivity cardiac troponin I (HScTnI, cutoff value <16 ng/L) was considered suggestive of acute myocardial damage when its value was at least one above the 99th percentile of the upper reference limit. A HSc-TnI higher than 200 ng/dl was calculated as the difference between the abnormal value and the normal value. C-reactive protein (CRP) was considered normal if the value was <10 mg/L. We considered a cardiovascular complication the first ischemic or thrombotic event during the hospitalization with COVID-19. Written informed consent was obtained by all participants. The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Padua University (CE 154n). Supporting data are available upon request.

**2.2 | CT scan protocol**

All CT scans were performed with a 64-slice CT system (Aquilion 64; Toshiba) and slice CT system (SOMATOM Sensation; Siemens). A Spiral non-electrocardiogram (ECG) gated technique during a deep inspiratory breath-hold was employed (tube voltage 120 kV, tube current power 50–200 mAs). Images were reconstructed with the following parameters: slice thickness 3 mm, the field of view 250–300 mm, convolution kernel filtering b30f. CAC score was performed on the workstation (Vitrea FX, version 1.0; Vital Images), using CAC score analysis software (VScore; Vital Images). Coronary calcium was defined as an area of at least three contiguous voxels in the axial plane in the course of the coronary artery, with an attenuation cutoff of ≥100 HU.

**2.3 | Calcium score analysis**

CAC score was performed offline (Vitrea FX, version 1.0; Vital Images), using CAC score analysis software (VScore; Vital Images).
Coronary calcium was defined as an area of at least three contiguous voxels in the axial plane in the course of the coronary artery, with an attenuation cut-off of $\geq 100$ HU (corresponding to a minimum lesion area $>1 \text{mm}^2$) in the 3.0 mm reconstruction.

Although the traditional Agatston method for measuring CAC requires ECG-gated acquisition, a good correlation has been demonstrated between CAC identified on non-gated CT scans and ordinal scores obtained from gated CT scans. Patient with Calcium were further stratified according to validated CAC score thresholds (1–100: mild; 101–400: moderate; >400: severe) and to the cutoff point of 10 (Table 1).

We evaluated the occurrence of complications including acute coronary syndrome (ACS), embolic events (cerebral or peripheral), pulmonary embolism, myocarditis, pericarditis, acute heart failure, septic shock, severe acute respiratory distress syndrome, acute kidney injury, and deep vein thrombosis. The primary endpoint was in-H mortality. The secondary endpoint was need for admission to the intensive care unit (ICU) and mechanical ventilation.

### 2.4 Statistical analysis

Descriptive statistics were reported as 1 quartile/median/III quartile for continuous data and percentages (absolute numbers) for categorical data.

Univariable and multivariable generalized linear models were estimated to assess the effect of baseline variables on the outcomes of interest using the Aranda link function, which was chosen because it was the parametrization that minimized the Bayesian information criterion. Multivariable model variable selection was made according to the Akaike information criterion.

The marginal effect was computed considering the partial derivatives of the marginal expectation. Results were reported as average marginal effect (AME), 95% confidence interval, and p-value. The AME expresses the change in probability of the event, that is, ICU admission, in-H mortality, mechanical ventilation.

### 3 RESULTS

Two-hundred-eighty-four patients were analysed.

Overall, the median age was 63, 25 years, 67% were males. Demographic, clinical, and laboratory features stratified by CAC status are presented in Table 2. Ordinal CAC score was calculated in 284 patients, 46 patients having mild (1–100), 39 moderate (101–400), and 57 severe (>400) CAC scores. However, we used only dichotomic values for statistical analysis (CAC = 0 was present in 142 patients, CAC $\geq 1$ was present in 142 patients) as we did not note any increase in the outcomes or in cardiovascular complications with increased CAC values.

As expected, factors associated with CAC were male sex, age, hypertension, diabetes, smoke, and previous CAD. Of note patients with CAC had a higher inflammatory burden at admission ($\gamma$-dimer, CRP, and procalcitonin) and higher HScTnI at admission and at peak. While there was no association with the presence of lung consolidations, patients with CAC had a higher incidence of bilateral pulmonary involvement and a trend towards worse GGO.

In-H mortality was associated with CAC. Nevertheless, it did not increase for each point increment in CAC. As expected, in-H mortality was associated with age but also with hypertension, hyperlipidaemia, obesity, and previous CAD. It was indeed related to lung consolidations and with a higher inflammatory response (Table 3A–C). Of note, peak HScTnI $>200$ ng/dl was positively associated with in-H mortality both at univariable and multivariable analysis.

CAC was not associated with the need of ICU admission and mechanical ventilation (Table 3A–C), whereas it appears that HScTnI $>200$ ng/L was associated with both.

Older age, hypertension, hyperlipidaemia, and smoking were positively associated with in-H mortality, need for ICU, and mechanical ventilation, also when considered as composite outcomes. The same increasing trend across the groups was observed for laboratory data at admission (CRP and HScTnI peak). In particular, CRP and HScTnI $>200$ ng/L remained positively associated with the composite outcome also in the multivariable model (Table 4).

### 4 DISCUSSION

Data from multiple cohorts shows that CAC effectively stratifies patients for long-term all-cause and cardiovascular mortality better than traditional risk factors. On the contrary, the effects of CAC on in-H mortality due to other causes, like sepsis, have been less explored.

The main finding of our study is the presence of calcium, was related to peak HScTnI. Peak HScTnI was linked with all the endpoints. CAC was associated with a higher rate of cardiovascular complications which was likely related to the increase in mortality. This association was not observed after correcting for traditional risk...
| Variable                      | CAC = 0 (N = 142) | CAC ≥ 1 (N = 142) | p    |
|-------------------------------|-------------------|-------------------|------|
| Male sex                      | 58%               | 77%               | .001 |
| Age (years)                   | 45.4/54.6/63.3    | 64.2/72.2/80.8    | <.001|
| Risk factors                  |                   |                   |      |
| Hypertension                  | 32%               | 69%               | <.001|
| Diabetes                      | 19%               | 27%               | .094 |
| Smoking                       | 9%                | 24%               | .001 |
| Obesity                       | 20%               | 20%               | .88  |
| Previous CAD                  | 3%                | 16%               | <.001|
| Chronic kidney disease        | 7%                | 11%               | .294 |
| Peripheral vasculopathy       | 6%                | 12%               | .059 |
| Pulmonary hypertension        | 1%                | 0%                | .156 |
| Chronic broncopneumopathy     | 5%                | 5%                | 1    |
| Previous malignancy           | 7%                | 12%               | .209 |
| Active malignancy             | 9%                | 10%               | .666 |
| Laboratory findings           |                   |                   |      |
| WBC × mm$^3$                  | 3.6/4.8/6.7       | 3.8/5.5/7.6       | .057 |
| Creatinine (mg/dl)            | 0.7/0.8/1.1       | 0.7/0.9/1.2       | .218 |
| D-dimer                       | 150/221/467       | 182/311/661       | .002 |
| CRP-admission (mg/L)          | 13/44/98          | 37/69/120         | .002 |
| Procalcitonin                 | 0.04/0.06/0.20    | 0.05/0.12/0.28    | .016 |
| SpO$_2$                       | 93/96/98          | 92/95/97          | .01  |
| HScTnI admission (ng/L)       | 2/5/10            | 7/14/38           | <.001|
| HScTnI peak (ng/L)            | 2/5/14            | 7/20/82           | <.001|
| Chest involvement             |                   |                   |      |
| Lung consolidation            | 64%               | 66%               | .673 |
| GGO                           | 78%               | 87%               | .055 |
| Bilateral involvement         | 81%               | 90%               | .043 |
| Complications                 |                   |                   |      |
| All cardiovascular complications | 24%             | 41%               | .004 |
| ACS                           | 9%                | 22%               | <.001|
| Major embolic event           | 1%                | 4                 | .194 |
| Pulmonary embolism            | 4%                | 9%                | .088 |
| Myocarditis                   | 1%                | 1%                | NA   |
| Pericarditis                  | 6%                | 10                | .348 |
| Acute heart failure           | 4%                | 9%                | .041 |
| Septic shock                  | 3%                | 5%                | .353 |
| Severe ARDS                   | 10%               | 12%               | .572 |
| Acute kidney injury           | 5%                | 10%               | .153 |
| DVT                           | 10%               | 18%               | .055 |
**Table 2** (Continued)

| Variable          | CAC = 0 (N = 142) | CAC ≥ 1 (N = 142) | p     |
|-------------------|-------------------|------------------|-------|
| **Treatment**     |                   |                  |       |
| Antibiotic use    | 95%               | 95%              | .967  |
| Antiviral use     | 30%               | 40%              | .101  |
| Hydroxychloroquine| 34%               | 28%              | .282  |
| Corticosteroids   | 54%               | 63%              | .105  |
| Tocilizumab       | 5%                | 6%               | .638  |
| Plasma            | 14%               | 17%              | .553  |
| **Outcomes**      |                   |                  |       |
| In-H mortality    | 7%                | 14%              | .048  |
| ICU               | 20%               | 24%              | .442  |
| Days in ICU       | 6/14/23           | 7/16/32          | .354  |
| Mechanical ventilation | 17%               | 20%              | .509  |

Note: Data are percentages for categorical variables and I quartile/median/III quartile for continuous variables.

Abbreviations: ACS, acute coronary syndrome; ARDS, acute respiratory distress syndrome; CAC, coronary artery calcium; CAD, coronary artery disease; CRP, C-reactive protein; DVT, deep vein thrombosis; GGO, ground-glass opacification; HScTnI, high-sensitivity cardiac troponin I; ICU, intensive care unit; in-H, in-hospital; NA, not applicable; WBC, white blood count.

**Table 3A** Outcome analysis: In-H mortality

| Variable                        | 0 (N = 249) | 1 (N = 29) | Average marginal effect (AME) | p     | Lower | Upper |
|---------------------------------|-------------|------------|-------------------------------|-------|-------|-------|
| CAC                             | 48%         | 68%        | 0.0725                        | .027  | 0.0079 | 0.1371|
| Age (years)                     | 51.4/61.9/74.1 | 67.7/74.8/83.7 | 0.0056                       | <.001 | 0.0031 | 0.0082|
| Male sex                        | 66%         | 79%        | −0.0571                       | .078  | −0.1205 | 0.0063|
| Hypertension                    | 46%         | 83%        | 0.1364                        | <.001 | 0.0653 | 0.2076|
| Diabetes                        | 23%         | 21%        | −0.0142                       | .717  | −0.0912 | 0.0627|
| Smoking                         | 15%         | 24%        | 0.0643                        | .24   | −0.043 | 0.1715|
| Obesity                         | 19%         | 23%        | 0.0198                        | .6792 | −0.074 | 0.1136|
| Dyslipidemia                    | 27%         | 52%        | 0.1111                        | .013  | 0.0233 | 0.1989|
| WBC                             | 3.785/5.130/7.030 | 3.330/4.270/7.860 | −0.0003                       | .942  | −0.009 | 0.0083|
| Creatinine (mg/dl)              | 0.7/0.840/1.100 | 0.7/1.0/1.2 | −0.0038                       | .548  | −0.0162 | 0.0086|
| CRP admission (mg/L)            | 20/59/96    | 60/98/130  | 0.0006                        | .008  | 0.0002 | 0.0011|
| Procalcitonin                   | 0.40/0.08/0.20 | 0.09/0.20/0.40 | 0.0178                        | .308  | −0.0164 | 0.052 |
| Saturation O₂%                  | 93/96/97    | 88/91/94   | −0.0093                       | .003  | −0.0154 | −0.0032|
| HScTnI admission                | 3.00/7.00/18.00 | 14.00/29.00/107.75 | 0    | .981 | −0.0003 | 0.0003|
| Lung consolidation              | 63%         | 82%        | 0.0805                        | .015  | 0.0155 | 0.1455|
| GGO                             | 81%         | 89%        | 0.0527                        | .091  | −0.0083 | 0.1138|
| Bilateral involvement           | 86%         | 93%        | 0.0575                        | .243  | −0.0391 | 0.154 |
| Antibiotic use                  | 94%         | 100%       | 0.1038                        | <.001 | 0.0691 | 0.1386|
| Antiviral use                   | 38%         | 22%        | −0.0607                       | .096  | −0.1322 | 0.0109|

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factors linked to worse COVID-19 outcomes such as age, diabetes, hypertension, and hyperlipidaemia.

4.1 | Comparison with previous studies

Our data are partially in agreement with Slipchuck et al., who compared baseline characteristics and outcomes of patients admitted with COVID-19 who had a CT study with patients who did not have a CT performed. Their patients had no previous history of percutaneous coronary intervention or coronary artery bypass grafting. They showed that for each point increase in CAC, mortality increased by 8% in 4 months follow-up. We did not find this association as we only tested in hospital mortality, not follow-up. In their study, CTs were obtained up to 5 years before index hospitalization, while in our study CTs were all done during admission to exclude CAC variation in our patients.

Gupta et al. demonstrated that CAC stratifies septic patients for cardiovascular complications better than traditional risk factors. CAC score was also evaluated in COVID-19 patients in smaller trials. Our data confirm the findings from an Italian cohort of patients (332 patients, 68 deaths and mortality of 20.5%) who found a correlation between CAC on admission and mortality that did not persist after multivariable correction. Compared to our study, patients in the study by Ferrante et al. had significantly lower comorbidities with less diabetes and hyperlipidaemia and lower incidence of CAC (CAC ≥ 1 of 43.9% vs. 50% in our study) and a lower incidence of events. Other small studies suggested a correlation of CAC and adverse events such as mechanical ventilation/extracorporeal membrane oxygenation or death. Our findings did not confirm these studies' hypothesis as we found no correlation between CAC and need for mechanical ventilation or admission to intensive care.

In the study by Scoccia et al., they spotted that clinical and subclinical CAD assessed by CAC score on a routine ECG non-gated
### Table 3B  Outcome analysis: ICU admission

| Variable                        | 0 (N = 219) | 1 (N = 63) | Average marginal effect (AME) | p       | Lower   | Upper   |
|---------------------------------|-------------|------------|------------------------------|---------|---------|---------|
| CAC                             | 49%         | 55%        | 0.0385                       | .495    | -0.0721 | 0.1491  |
| Age (years)                     | 51.450/62.100/76.700 | 56.500/67.300/73.850 | 0.0022 | .057    | -0.0001 | 0.0046  |
| Male sex                        | 65%         | 76%        | -0.0865                      | .053    | -0.1741 | 0.0011  |
| Hypertension                    | 46%         | 67%        | 0.1458                       | .001    | 0.0634  | 0.2282  |
| Diabetes                        | 21%         | 25%        | 0.0394                       | .52     | -0.0804 | 0.1591  |
| Smoking                         | 14%         | 25%        | 0.1478                       | .056    | -0.0038 | 0.2994  |
| Obesity                         | 20%         | 20%        | 0.0029                       | .9647   | -0.1272 | 0.1330  |
| Dyslipidemia                    | 28%         | 38%        | 0.0844                       | .052    | -0.0006 | 0.1693  |
| WBC × mm³                       | 3.7/4.9/6.8 | 3.9/5.5/10.9 | 0.0107                      | .079    | -0.0012 | 0.0226  |
| Creatinine (mg/dl)              | 0.7200/0.8000/1.0700 | 0.7300/0.9100/1.2825 | -0.0033 | .705    | -0.0205 | 0.0138  |
| CRP admission (mg/L)            | 17/55/89    | 58/100/160 | 0.0018                       | <.001   | 0.0012  | 0.0025  |
| Procalcitonin                   | 0.0400/0.0600/0.1525 | 0.0975/0.2700/0.4825 | 0.0003 | .994    | -0.073  | 0.0736  |
| Saturation O₂                   | 93/96/97    | 88/92/95   | -0.0213                      | .001    | -0.0333 | -0.0092 |
| HSCTnI admission (ng/L)         | 3/6/18      | 8/14/40    | 0                            | .945    | -0.0007 | 0.0008  |
| consolidation                   | 14%         | 25%        | 0.1478                       | .056    | -0.0038 | 0.2994  |
| GGO                             | 79%         | 94%        | 0.1836                       | <.001   | 0.1008  | 0.2665  |
| Bilateral infiltration          | 83%         | 97%        | 0.2077                       | <.001   | 0.1248  | 0.2906  |
| Antibiotic use                  | 94%         | 100%       | 0.2293                       | <.001   | 0.1749  | 0.2837  |
| Antiviral use                   | 35%         | 38%        | 0.0189                       | .746    | -0.0954 | 0.1332  |
| Hydroxychloroquine              | 35%         | 18%        | -0.134                       | .001    | -0.2147 | -0.0533 |
| Corticosteroids                 | 53%         | 79%        | 0.1806                       | <.001   | 0.0854  | 0.2759  |
| Tocilizumab                     | 5%          | 7%         | 0.0341                       | .774    | -0.1988 | 0.267   |
| Plasma transfusion              | 13%         | 25%        | 0.146                        | .031    | 0.013   | 0.279   |
| D-dimer >1000                   | 10%         | 18%        | 0.1670                       | .028    | 0.0180  | 0.3160  |
| Peak HSCTnI 34–200              | 12%         | 21%        | 0.2030                       | .0338   | 0.0155  | 0.3905  |
| Peak HSCTnI >200                | 5%          | 26%        | 0.4470                       | <.001   | 0.2468  | 0.6471  |
| Previous CAD                    | 9%          | 13%        | 0.0666                       | .4275   | -0.0976 | 0.2311  |
| Chronic kidney disease          | 8%          | 14%        | 0.116                        | .2873   | -0.0976 | 0.3296  |
| Peripheral vasculopathy         | 7%          | 17%        | 0.1878                       | .09081  | -0.0298 | 0.4055  |
| Pulmonary hypertension          | 0%          | 2%         |                              |         |         |         |
| Chronic broncpenepathomy        | 4%          | 8%         | 0.1502                       | .2977   | -0.1325 | 0.433   |
| Previous malignancy             | 9%          | 12%        | 0.05042                      | .6034   | -0.1398 | 0.2407  |
| Active malignancy               | 10%         | 8%         | -0.02369                     | .7462   | -0.1672 | 0.1198  |

Multivariate analysis: Data are AME, p (p-value), and lower and upper bound of the 95% confidence interval

| Variable                        | AME       | p     | Lower   | Upper   |
|---------------------------------|-----------|-------|---------|---------|
| Antibiotics                     | 0.2554    | <.001 | 0.1979  | 0.3129  |
| Bilateral infiltrates           | 0.1632    | .008  | 0.0426  | 0.2839  |
| Peak HSCTnI 34–200              | 0.1788    | .031  | 0.0164  | 0.3412  |

(Continues)
TABLE 3B (Continued)

| Variable                  | AME  | p    | Lower   | Upper   |
|---------------------------|------|------|---------|---------|
| Peak HScTnI >200          | 0.3350 | 0.002 | 0.1273  | 0.5428  |
| Saturation O₂             | -0.0147 | 0.030 | -0.0279 | -0.0014 |

Note: Data are percentages for categorical variables and I quartile/median/III quartile for continuous variables. The table also reports the results of the univariate models, as AME, p (p-value), and lower and upper bound of the 95% confidence interval.

Abbreviations: CAC, coronary artery calcium; CAD, coronary artery disease; CRP, C-reactive protein; GGO, ground-glass opacification; HScTnI, high-sensitivity cardiac troponin I; ICU, intensive care unit; WBC, white blood count.

TABLE 3C   Outcome analysis: Mechanical ventilation

| Variable                  | 0 (N = 229) | 1 (N = 52) | Average marginal effect (AME) | p    | Lower   | Upper   |
|---------------------------|-------------|------------|-------------------------------|------|---------|---------|
| CAC 50%                   | 55%         | 0.0309     | .583                          | -0.0794 | 0.1412  |
| Age (years) 51.2/62.2/76.6 | 57.3/67.0/73.2 | 0.0022     | .026                          | 0.0003  | 0.0042  |
| Male sex 65%               | 81%         | -0.1088    | .007                          | -0.1877 | -0.0299 |
| Hypertension 46%           | 69%         | 0.141      | <.001                         | 0.0706  | 0.2115  |
| Diabetes 23%               | 21%         | -0.0135    | .798                          | -0.1168 | 0.0899  |
| Smoking 14%                | 25%         | 0.1159     | .13                           | -0.0341 | 0.266   |
| Obesity 21%                | 16%         | -0.0429    | .4497                         | -0.1541 | 0.0683  |
| Dyslipidemia 28%           | 38%         | 0.072      | .121                          | -0.0191 | 0.1631  |
| WBC × mm³ 3.7/5.1/7.0      | 3.8/5.0/11.0 | 0.0066     | .199                          | -0.0035 | 0.0167  |
| Creatinine (mg/dl) 0.7225/0.8200/1.0675 | 0.7000/0.9700/1.3250 | -0.0019    | .821                          | -0.0182 | 0.0145  |
| CRP-admission (mg/L) 18/56/91 | 59/100/160 | 0.0015     | <.001                         | 0.0009  | 0.0021  |
| Procalcitonin 0.04/0.65/0.16 | 0.10/0.27/0.49 | 0.001      | .975                          | -0.0638 | 0.0658  |
| Saturation O₂ 93/96/97     | 88/92/95    | -0.0174    | .001                          | -0.0279 | -0.0068 |
| HScTnI admission 3/6/20    | 8.275/14.000/30.000 | 0          | .974                          | -0.0005 | 0.0005  |
| Lung consolidations 61%    | 85%         | 0.164      | .001                          | 0.0635  | 0.2644  |
| GGO 79%                    | 94%         | 0.1602     | <.001                         | 0.0775  | 0.2429  |
| Bilateral involvement 83%  | 98%         | 0.1928     | <.001                         | 0.1154  | 0.2702  |
| Antibiotic use 94%         | 100%        | 0.1917     | <.001                         | 0.1475  | 0.236   |
| Antiviral use 36%          | 33%         | -0.0189    | .721                          | -0.1225 | 0.0848  |
| Hydroxychloroquine 35%     | 14%         | -0.1487    | <.001                         | -0.215  | -0.0824 |
| corticosteroids 54%        | 80%         | 0.1638     | <.001                         | 0.0793  | 0.2483  |
| Tocilizumab 6%             | 4%          | -0.0606    | .507                          | -0.2398 | 0.1186  |
| Plasma transfusion 13%     | 27%         | 0.1614     | .006                          | 0.0459  | 0.2769  |
| D-dimer 500–1000 16%       | 18%         | 0.0421     | .064                          | -0.0839 | 0.1681  |
| D-dimer >1000 9%           | 20%         | 0.1709     | .020                          | 0.0271  | 0.3147  |
| Peak HScTnI 34–200 12%     | 20%         | 0.1481     | .0863                         | -0.0212 | 0.3175  |
| Peak HScTnI >200 6%        | 28%         | 0.4009     | <.001                         | 0.1859  | 0.6159  |
| Previous CAD 10%           | 10%         | -0.0021    | .9796                         | -0.1605 | 0.1564  |
chest CT are associated with in-H mortality and myocardial infarction/cerebrovascular accident. They also discovered that traditional cardiovascular risk factors are not independently associated with COVID-19 in-H mortality when the extent and presence of coronary atherosclerosis is considered. On the contrary, in our study, on the multivariable analysis emerged that high peak troponin was significantly correlated with in hospital mortality and other outcomes, indicating that CAC does not completely identify patients at risk of cardiovascular events because probably it does not reveal soft, unstable plaques that are more sensitive to external stresses.30

4.2 | Limitations of CAC score

Studies have shown that there is an increase in noncalcified plaque volumes in ACS patients. Moreover, when coronary computed tomography angiography plaque features are accounted for, patients with widespread nonobstructive CAD had similar event rates compared with patients with localized obstructive disease, suggesting that plaque characteristics are important in defining accurate cardiovascular risk beyond calcifications.30

The main finding of our research is that CAC alone does not completely identify all the population at risk of cardiovascular events in the setting of COVID-19 patients. On the other hand, HsCtTnI was a better determinant of outcomes.10,29 Therefore, it could be hypothesized that other factors, including the presence of soft plaques, may be a substratum where hypoxemia, systemic inflammation, endothelial injury triggered by direct virus activity through angiotensin-converting enzyme 2 endothelial receptor, followed by platelet activation triggers cardiovascular events,31 thus increasing the rate of adverse outcomes.

5 | CONCLUSION

Our findings demonstrated that peak HsCtTnI is linked with all the endpoints in COVID-19 patients. CAC score was not, per se, the strongest marker for the considered endpoints. This arises the possibility CAC score may slightly underestimate the risk of adverse events. These findings support the conduct of larger trials on cardiovascular disease potentially in other infectious and inflammatory diseases.

5.1 | Limitations

The study’s inclusion criteria of infected patients who had a chest CT selected a higher-risk population, reflected in the higher mortality
### TABLE 4  Composite outcome: Death, ICU admission, and mechanical ventilation

| Variable                        | 0 (N = 206) | 1 (N = 74) | Average marginal effect (AME) | p     | Lower | Upper |
|---------------------------------|-------------|------------|--------------------------------|-------|-------|-------|
| CAC                             | 48%         | 57%        | 0.067                          | .247  | −0.0464 | 0.1805 |
| Age                             | 51.250/61.850/75.025 | 58.075/68.650/76.675 | 0.0049                         | <.001 | 0.0022 | 0.0075 |
| Male sex                        | 65%         | 76%        | −0.0947                        | .077  | −0.1999 | 0.0104 |
| Hypertension                    | 44%         | 68%        | 0.1819                         | <.001 | 0.0801 | 0.2838 |
| Diabetes                        | 22%         | 24%        | 0.0276                         | .666  | −0.0979 | 0.1532 |
| Smoking                         | 14%         | 24%        | 0.151                          | .046  | 0.003  | 0.299  |
| Obesity                         | 20%         | 18%        | −0.0205                        | .7703 | −0.1583 | 0.1172 |
| Dyslipidemia                    | 26%         | 42%        | 0.1497                         | .016  | 0.0278 | 0.2715 |
| WBC                             | 3.7400/4.9000/6.7300 | 3.7950/5.4800/10.7375 | 0.0121                         | .067  | −0.0009 | 0.0252 |
| Creatinine (mg/dl)              | 0.720/0.800/1.065 | 0.760/0.920/1.300 | −0.0044                        | .475  | −0.0165 | 0.0077 |
| CRP admission (mg/L)            | 16.00/50.50/87.25 | 59.25/100.00/157.50 | 0.0021                         | <.001 | 0.0013 | 0.0029 |
| Procalcitonin                   | 0.0400/0.0600/0.1500 | 0.0800/0.2300/0.4600 | 0.0397                         | .43   | −0.0589 | 0.1383 |
| Saturation O₂                   | 94/96/97    | 88/92/95   | −0.0276                        | .001  | −0.0439 | −0.0113 |
| Consolidation                   | 61%         | 79%        | 0.1665                         | .001  | 0.0713 | 0.2617 |
| GGO                             | 79%         | 90%        | 0.1555                         | .014  | 0.0311 | 0.28   |
| Bilateral infiltration          | 83%         | 96%        | 0.2184                         | <.001 | 0.1167 | 0.3201 |
| Antibiotics                     | 93%         | 100%       | 0.2727                         | <.001 | 0.2308 | 0.3147 |
| Antiviral                       | 36%         | 35%        | −0.014                         | .815  | −0.1316 | 0.1035 |
| Hydroxychloroquine              | 35%         | 22%        | −0.1108                        | .029  | −0.2103 | −0.0113 |
| Corticosteroids                 | 52%         | 78%        | 0.2044                         | <.001 | 0.0968 | 0.312  |
| Tocilizumab                     | 6%          | 6%         | −0.0095                        | .941  | −0.2635 | 0.2444 |
| Plasma                          | 14%         | 22%        | 0.1243                         | .119  | −0.0321 | 0.2808 |
| d-dimer 500–1000                | 14%         | 22%        | 0.1585                         | .054  | −0.0029 | 0.3199 |
| d-dimer >1000                   | 7%          | 23%        | 0.3433                         | <.001 | 0.1654 | 0.5211 |
| Peak HScTnI 34–200              | 10%         | 24%        | 0.3155                         | .002  | 0.1205 | 0.5105 |
| Peak HScTnI>200                 | 3%          | 30%        | 0.6375                         | <.001 | 0.4735 | 0.8014 |
| Previous CAD                    | 8%          | 15%        | 0.1398                         | .1938 | −0.0711 | 0.3508 |
| Chronic kidney disease          | 8%          | 13%        | 0.114                          | .2753 | −0.0908 | 0.3189 |
| Peripheral vasculopathy         | 7%          | 16%        | 0.1842                         | .07392 | −0.0178 | 0.3862 |
| Pulmonary Hypertension          | 0%          | 1%         |                                |       |        |       |
| Chronic broncopneumopathy       | 3%          | 10%        | 0.2568                         | .03475 | 0.0184 | 0.4951 |
| Previous malignancy             | 9%          | 11%        | 0.05769                        | .4664 | −0.09756 | 0.2129 |
| Active malignancy               | 9%          | 11%        | 0.05769                        | .5073 | −0.1128 | 0.2282 |

Multivariate analysis: Data are AME, p (p-value), and lower and upper bound of the 95% confidence Interval

| Variable                        | AME         | p        | Lower     | Upper     |
|---------------------------------|-------------|----------|-----------|-----------|
| Antibiotic                      | 0.2865      | <.001    | 0.2258    | 0.3472    |
| CRP                             | 0.0013      | <.001    | 0.0007    | 0.0018    |
| Peak HScTnI 34–200              | 0.2439      | .005     | 0.0737    | 0.4140    |
rate. We did not consider in our analysis the impact of CAC in patients with milder infection.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS
Valeria Pergola: Conceptualization, methodology, and writing – original draft preparation. Giulio Cabrelle: Conceptualization, methodology, and writing – original draft preparation. Giulio Barbiero and Andrea Fiorwncis: Investigation and methodology. Chiara Giraudo and Marco Previdiero: Data curation and software. Carlo M. Dellino, Carolina Montonati, and Saverio Continisio: Visualization and investigation. Donato Mele and Martina Perazzolo Marra: Supervision: Giulia Lorenzoni and Elisa Masetto: Software and formal analysis. Giovanni Di Salvo and Dario Gregorio: Formal analysis and validation: Raffaella Motta and Sabino Iliceto: Writing – reviewing and editing (equally contributed).

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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TABLE 4 (Continued)

| Variable | AME | p   | Lower | Upper |
|----------|-----|-----|-------|-------|
| Peak HScTnI>200 | 0.4801 | <.001 | 0.2891 | 0.6711 |
| Saturation $O_2$ | $-0.0154$ | .022 | $-0.0286$ | $-0.0023$ |
| Chronic broncopneumopathy | 0.2568 | .03475 | 0.0184 | 0.4951 |

Note: Data are percentages for categorical variables and I quartile/median/III quartile for continuous variables. The table also reports the results of the univariable models, as AME, $p$ (p-value), and lower and upper bound of the 95% confidence Interval.

Abbreviations: CAC, coronary artery calcium; CAD, coronary artery disease; CRP, C-reactive protein; GGO, ground-glass opacification; HScTnI, high-sensitivity cardiac troponin I; ICU, intensive care unit; WBC, white blood count.
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