Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Teaching an old dog new tricks: The prognostic role of CACS in hospitalized COVID-19 patients

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In this issue of *Atherosclerosis*, Scoccia et al. present an interesting study on the prognostic role of coronary artery calcium scores (CACS) in COVID-19 [1]. They used a large unselected population of patients hospitalized in 16 Italian hospitals for severe COVID-19. CACS were computed from clinically indicated non-gated chest computed tomography (CT) scans and patients were divided into 3 categories of coronary artery disease (CAD): no CAD (CACS = 0), prior CAD (history of previous surgical or percutaneous coronary revascularization) or subclinical CAD (further classified based on CACS as mild: ≤100; moderate: 100–400; and severe: >400). After a mean follow-up of 14 days, in-hospital death (primary outcome) occurred in 385 (23.7%) patients while in-hospital myocardial infarction or cerebrovascular accident (secondary outcome) occurred in 39 (2.4%) patients. In multivariable Cox regression models adjusted for several clinical risk-factors, patients with sub-clinical and clinical CAD had a statistically significant higher risk for a primary outcome when compared to those with no CAD. CACS on a continuous scale and using pre-defined thresholds in those with subclinical CAD were also significantly associated with worst outcomes. A similar association was seen using the secondary outcome and on sensitivity analyses stratifying by age groups. Furthermore, the use of CAD categories significantly improved model discrimination (assessed through Harell's C test) when compared to models with clinical variables and markers of COVID-19 disease severity. Lastly, established risk factors were no longer predictive of outcomes when taking into account CACS.

Never before has risk prediction been more important than during the current COVID-19 pandemic. Since the start of the pandemic in early December 2019, over 136 million cases and nearly 3 million deaths have been recorded to date [2]. The pandemic is overwhelming healthcare systems and the need to allocate limited resources to tailor management has been the main driving force for research on risk prediction. There are now a multitude of studies that have shown the role of established and novel markers of prognosis in patients with COVID-19 [3].

Research spanning the past 3 decades has firmly established the role of CACS in personalized management of asymptomatic patients with CAD. Multiple cohort studies consisting of over 100,000 patients have shown the association of high CACS with incident cardiovascular outcomes, and a CACS = 0 is associated with a very low risk of incident events [4]. CACS is endorsed in American guidelines as a class IIa test to guide management in asymptomatic patients at intermediate risk of CAD [5]. Furthermore, recent studies have identified novel areas were CACS can be applied, such as predicting competing cause of death across age groups and improving the efficiency of clinical trials [6,7].

The data presented by Scoccia et al. [1] further add to prior literature in expanding a novel use of CACS by showing a link with COVID-19 outcomes. On a pathophysiologic basis, such a link is plausible as CACS is a marker of the cumulative vascular damage brought by prolonged exposure to risk factors. Myocardial injury, particularly Type II myocardial infarction caused by demand ischemia, has been shown to be significantly associated with poor outcomes in patients with COVID-19 [8,9]. Patients with a high plaque burden reflected by high CACS are at increased risk for plaque rupture during physiologic stress such as that from severe COVID-19 disease [10]. The hypercoagulable state associated with the active phase of COVID-19 infection can expand thrombus formation during plaque rupture [11]. More broadly, CACS could be a reflection of the overall health of patients and may account for unmeasured confounders.

The association of CACS with outcomes of acute illnesses from infectious diseases is not unique to COVID-19. Prior studies have shown CACS predict cardiovascular complications in patients with sepsis, are

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highly associated with *H. pylori* infection, and identify those at higher risk of acquiring pneumonia [12–14].

Although this study is not the first to show the association of CACS with COVID-19, it is the largest reported cohort. Dillinger et al. [15] used non-gated CT scans from 209 consecutive hospitalized patients with COVID-19 and showed how the presence of any plaque and quantitative CACS (Agatston score) were significantly associated with the primary outcome of mechanical noninvasive or invasive ventilation, extracorporeal membrane oxygenation, or death. Similar associations were seen after stratifying by age group and in multivariable models adjusting for demographic variables and cardiovascular risk factors (hypertension, diabetes and smoking). Of note, even though coronary artery calcium was detected in half (50.7%) of the patients in the Dillinger study [15], the overall plaque burden was relatively low with a median CACS of 8 (IQR: 0–116) [15]. Recently, Gupta et al. [16] conducted a similar study on 108 hospitalized patients with COVID-19 and showed that CACS were associated with the primary outcome of intubation/death, and the secondary outcome of elevated D-dimer. Similar to the study by Dillinger [15], they found both the presence of calcified plaque and extent of plaque were associated with worst outcomes even after adjusting for a broad set of demographic, clinical and laboratory covariates. However, two points of difference in Gupta et al. [16] when compared to the Dillinger study [15] are the use of non-gated CT scans done within 3 months prior to or after admission, and CACS quantification using an ordinal scoring method [17].

There are several points in the current study that merit discussion when trying to translate the findings to clinical practice. Since all included patients were submitted to non-gated chest CT scanning, it is difficult to surmise whether these results apply to all hospitalized patients with COVID-19. Knowing what proportion of all hospitalized patients had an indication for a non-gated chest CT scan, and a better description of the guidelines used for the selection of such patients might have helped better gauge the degree of selection bias. Second, it is curious that most of the established risk factors included in the multivariable models were no longer significant when CACS were added. Prior studies have shown that CACS provide incremental prognostic information beyond risk factors. However, it is difficult to conceive that adding CACS alone invalidates all other measures. These findings may have arisen as a result of a statistical issue (such as collinearity) or unique aspects of the study population. Lastly, the authors provide us with an incomplete picture of the clinical severity of COVID-19 disease in the cohort. Although cardiovascular risk factors are provided, details such as degree of hypoxia and APACHE scores would have provided the reader with a more holistic picture of the clinical condition of the patients studied. The inclusion of such variables in the final multivariable models would have also increased the robustness of findings.

This study also highlights an important insight for clinical practice. Since non-gated CT scans are commonly done in patients with severe COVID-19 (to gauge the degree of lung damage, to assess for complications and to monitor progression), a routine reporting of CACS in such patients might provide relevant prognostic information without incurring additional costs. The study also points at two areas of potential future research. First, having identified high-risk patients, the natural question is whether an intensification of management in such patients may reduce risk of events. Observational studies such as the present one cannot provide such proof of concept, and only randomized clinical trial might be able to address this important question. On a technical plane, the authors added to the existing literature that has shown the inter-observer reproducibility of non-gated CT scans for CACS calculation [18,19]. This raises the question as to whether gating all chest CT scans is truly necessary.

In conclusion, Scoccia et al. provide us with an important and timely study on the use of an established risk stratification tool in a new patient cohort. Their findings have important and potentially practice changing implications in the imaging evaluation and management of patients hospitalized with COVID-19 and highlight pertinent areas for future research. As successive waves of SARS-CoV-2 continue to affect countries across the globe, studies such as this will help clinicians and health systems to allocate resources and tailor management, ultimately contributing towards improved outcomes.

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.

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Ahmed Ibrahim Ahmed
Houston Methodist Debakey Heart & Vascular Center, Houston, TX, USA

Paolo Raggi
University of Alberta, Edmonton, AB, Canada

Mouaz H. Al-Mallah*
Houston Methodist Debakey Heart & Vascular Center, Houston, TX, USA

* Corresponding author. Weill Cornell Medical College, Houston Methodist DeBakey Heart & Vascular Center, 6550 Fannin Street, Smith Tower - Suite 1801, Houston, TX, 77030, USA.
E-mail address: mal-mallah@houstonmethodist.org (M.H. Al-Mallah).