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Original Article

Association between Coronary Artery Calcium Burden and Multiple Organ Dysfunction Syndrome in Critically Ill Patients with COVID-19

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Highlights

- CAC on non-gated chest CT correlated positively with SOFA scores in severe COVID-19.
- The association between CAC and organ failure was more pronounced without comorbidities.
- CAC was not an independent predictor of MODS after multivariable adjustment (P=0.912).
- Age and chronic kidney disease were the primary independent drivers of organ failure.

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ABSTRACT

Background: In this study, we aimed to examine the association between coronary artery calcium (CAC) burden and the severity of multiple organ dysfunction syndrome (MODS) in mechanically ventilated patients with COVID-19.

Methods: We retrospectively evaluated 160 patients with COVID-19 who required invasive mechanical ventilation and were admitted to the intensive care unit. CAC was assessed visually on nongated, noncontrast chest computed tomography (CT) using a semiquantitative Weston scoring system. The extent of organ dysfunction was quantified using the Sequential Organ Failure Assessment (SOFA) score. Associations between CAC burden and SOFA score were examined using the Pearson correlation and one-way analysis of variance, while independent associations were evaluated using multivariable linear regression.

Results: The mean (SD) SOFA score was 5.15 (2.73), and the mean (SD) CAC burden was 4.02 (3.31). In the overall cohort, CAC burden was positively correlated with SOFA score (r=.260; P=.001). This association was more pronounced among patients without pre-existing comorbidities (r=.402; P=.002). However, CAC burden was not independently associated with SOFA score in the multivariable regression model (β=0.009; P=.91). Age (β=0.043; P=.01) and chronic kidney disease (β=2.648; P<.001) were the principal independent correlates of SOFA score after adjustment for clinical covariates.

Conclusion: Although higher CAC burden was associated with higher SOFA scores in unadjusted analyses, this relationship was not independent after multivariable adjustment. CAC assessment on nongated chest CT may provide contextual information regarding underlying vascular disease; however, it should not be interpreted as an isolated marker of organ dysfunction severity, and its incremental clinical value requires confirmation in larger prospective studies.

Keywords: COVID-19; Coronary Artery Calcification (CAC); SOFA Score; Mechanical Ventilation; Chest CT; Multiple Organ Dysfunction Syndrome

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Introduction

COVID-19, caused by SARS-CoV-2, was declared a pandemic in early 2020.[1] The COVID-19 pandemic has imposed a substantial global health burden, while excess mortality analyses indicate that the true number of attributable deaths likely exceeded officially reported estimates in many settings.[2] Although COVID-19 predominantly presents with respiratory involvement, it is now recognized as a systemic disease with clinically important extrapulmonary manifestations.[3-5] Gastrointestinal and neurological complications may also occur, particularly in severe disease.[6,7] COVID-19 has been associated with a broad spectrum of cardiovascular complications, particularly among patients with pre-existing cardiovascular risk factors.[8]

Baseline cardiovascular status has been identified as a critical determinant of clinical recovery, with pre-existing disease associated with increased morbidity in COVID-19. Early epidemiologic data reported substantially higher case fatality rates among patients with underlying cardiovascular comorbidity,[9] and subsequent clinical studies similarly identified prior cardiovascular disease and related factors as being associated with increased mortality risk.[10,11] Coronary artery calcification (CAC), a computed tomography (CT)–based marker of underlying atherosclerotic disease, has long been used for cardiovascular risk stratification and has demonstrated prognostic value for adverse cardiovascular events and all-cause mortality.[12-14] In COVID-19 cohorts, higher CAC burden has also been linked to in-hospital death and other adverse outcomes.[15]

Because chest CT is frequently obtained in hospitalized patients with COVID-19, incidental CAC assessment may offer a readily available indicator of baseline cardiovascular vulnerability without additional imaging or radiation exposure. However, existing evidence remains heterogeneous and is often derived from mixed severity populations. Moreover, data focusing on critically ill patients requiring invasive mechanical ventilation and using standardized measures of organ dysfunction are limited. Multiple organ dysfunction syndrome (MODS) frequently complicates the clinical course of patients requiring invasive mechanical ventilation and is strongly predictive of poor clinical outcomes. The Sequential Organ Failure Assessment (SOFA) score is a validated and widely used tool to quantify the extent of organ dysfunction in critical illness.

Accordingly, in this retrospective, single-center observational study of mechanically ventilated patients with polymerase chain reaction (PCR)–confirmed COVID-19 admitted to the intensive care unit (ICU), we aimed to evaluate the association between the extent of CAC on chest CT and the severity of MODS as measured by the SOFA score. We hypothesized that a higher CAC burden, quantified using the semiquantitative Weston score, would be associated with a higher SOFA score

Methods

Study Design and Setting

This retrospective, single-center observational study was conducted at Ali-ibne-Abitaleb Hospital, Zahedan, Iran, and included mechanically ventilated patients with laboratory-confirmed COVID-19 hospitalized between 2020 and 2022.

Participants

Eligible patients were adults with PCR–confirmed COVID-19 who required invasive mechanical ventilation and had undergone nongated, noncontrast chest CT for clinical indications during the index hospitalization. Patients were excluded if CT images were not available or if the medical record contained incomplete key clinical data required for analysis.

Of 242 mechanically ventilated patients screened, 65 were excluded because of the absence of chest CT imaging, and 17 were excluded because of incomplete clinical data. Consequently, the final analytic cohort comprised 160 patients. A complete-case analysis was performed, and no missing data were imputed.

Coronary Artery Calcium (CAC) Assessment

CAC burden was assessed on nongated, noncontrast chest CT using the Weston score.16-

22 Each of the 4 major coronary arteries-the left main, left anterior descending, left circumflex, and right coronary artery-was graded according to the longitudinal extent of visible calcification: 0, no calcification; 1, less than one-third of vessel length; 2, one-third to two-thirds; and 3, greater than two-thirds. The vessel scores were summed to yield a total Weston score ranging from 0 to 12. For categorical analysis, scores were stratified into mild (0-4), moderate (5-8), and severe (9-12) CAC burden categories.

Assessment of MODS

The extent of organ dysfunction was quantified using the SOFA score, which was used in this study as the operational measure of MODS severity.[23] The SOFA score grades dysfunction across 6 organ systems-respiratory, cardiovascular, renal, hepatic, coagulation, and neurologic-with each system scored from 0 (normal) to 4 (most severe dysfunction), yielding a total score ranging from 0 to 24; higher scores reflect more severe organ dysfunction and worse prognosis.[23] The SOFA score was calculated on the first day of ICU admission based on standard definitions and the worst values recorded during the preceding 24 hours.

Assessment of Comorbid Conditions

Baseline comorbidities were retrieved from the patients' medical records at ICU admission. The evaluated conditions included hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, chronic liver disease, and chronic pulmonary disease. Each comorbidity was recorded as present or absent based on a previously documented diagnosis in the medical record and/or the use of disease-specific medication before ICU admission. The frequency and proportion of each comorbidity in the study population are presented in (Table 1).

Data Sources and Covariates

Demographic characteristics and baseline clinical variables were extracted from the hospital electronic medical records, including age, sex, and documented comorbidities, as well as relevant laboratory variables recorded during routine clinical care.

Statistical Analysis

Continuous variables were summarized as mean (SD) and, where informative, as median (IQR). Categorical variables were presented as number (percentage). The association between CAC burden and the severity of organ dysfunction, assessed using the SOFA score, was evaluated using both categorical and continuous approaches.

CAC was analyzed both categorically and continuously to provide complementary descriptive and inferential perspectives. Categorical grouping facilitated comparison of mean SOFA scores across clinically interpretable CAC strata, whereas continuous modeling preserved the full variability of the Weston score and allowed multivariable adjustment for potential confounders. For the categorical analysis, patients were classified into 3 CAC burden groups-mild, moderate, and severe-according to the semiquantitative Weston scoring system. Differences in mean SOFA scores among the 3 groups were assessed using one-way analysis of variance (ANOVA).

Exploratory Pearson correlation analyses were performed within subgroups defined by sex, age, duration of hospitalization, and the presence of pre-existing comorbidities. These analyses were not adjusted for potential confounders or multiple comparisons and were therefore considered hypothesis-generating.

For the continuous analysis, multivariable linear regression analysis was performed to evaluate the independent association between the continuous Weston CAC score and the SOFA score after adjustment for age, sex, hypertension, diabetes mellitus, dyslipidemia, kidney disease, liver disease, and lung disease. The regression results were reported as regression coefficients with corresponding 95% CIs and two-sided P values, where applicable. Statistical significance was defined as a two-sided P value of less than .05. All analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp, Armonk, NY).

Results

Study Population and Baseline Characteristics

A total of 242 patients with COVID-19 requiring invasive mechanical ventilation were screened. Upon screening patients against our established eligibility and exclusion criteria-specifically the absence of CT imaging (n=65) and incomplete medical records (n=17)-the final cohort consisted of 160 patients. The mean (SD) age was 61.08 (16.22) years (range, 20-90 y), with a male predominance (n=92, 57.5%). Comorbidities were present in 105 patients (65.6%), while 55 patients (34.4%) had no underlying diseases (Table 1).

Subgroup Analysis: Correlation Between CAC and SOFA Scores

To characterize the relationship between CAC burden and SOFA score across clinically relevant strata, Pearson correlation analyses were performed (Table 2). In the overall cohort, CAC burden showed a modest but significant positive correlation with SOFA score (r=.260; P=.001). In sex-stratified analysis, a statistically significant positive correlation was observed in male patients (r=.230; P=.03), whereas the correlation did not reach statistical significance in female patients (r=.139; P=.26).

Stratification by duration of hospitalization revealed that CAC burden was significantly correlated with SOFA score only among patients with a shorter hospital stay (<10 d; r=.297; P=.002). No significant correlation was found in patients with prolonged hospitalization (≥10 d; r=.031; P=.82). With regard to underlying health status, CAC burden showed a significant positive correlation with SOFA score only in patients without comorbid conditions (r=.402; P=.002), whereas this correlation was not significant in patients with at least 1 underlying disease (r=.087; P=.38). Age-stratified analysis demonstrated no statistically significant correlation between CAC burden and the SOFA score in either patients aged below 60 years (r=.173; P=.16) or those aged 60 years or more (r=.069; P=.51).

Association Between CAC Burden and Mean SOFA Score

(Table 3) summarizes the mean SOFA scores stratified by CAC burden category. Mean SOFA scores differed significantly across CAC burden categories, being lowest in the mild group (0–4; mean [SD], 4.63 [2.58]) and higher in the moderate (5–8; 6.02 [2.61]) and severe (9–12; 5.95 [3.15]) groups (one-way ANOVA, $F_{2,157} = 5.029$; P=.008). Post hoc Tukey testing identified a significant pairwise difference only between the moderate and mild groups (mean difference, 1.398; adjusted P=.02); no other pairwise comparison reached significance.

Multivariable Linear Regression

These bivariate findings were not reproduced in the multivariable linear regression model, in which CAC burden did not retain an independent association with SOFA score after adjustment for age, sex, and comorbidities (β=0.009; P=.91) (Table 4). Among the covariates examined, only age (β=0.043; P=.01) and chronic kidney disease (β=2.648; P<.001) remained independently associated with higher SOFA scores. Therefore, the apparent subgroup correlations should be interpreted with caution and considered exploratory.

Table 1. Baseline clinical characteristics of mechanically ventilated patients with COVID-19 (No.=160)

Characteristic	Value
Age, y	61.08 (16.22); 62 (51–72); 20–90
Age ≥60 y	92 (57.5)
Sex, male	92 (57.5)
Sex, female	68 (42.5)
Hospitalization, d	8.32 (6.31); 7 (3–12); 1–36

Hospitalization ≥10 d	56 (35.0)
Hypertension	79 (49.4)
Diabetes	58 (36.3)
Dyslipidemia	33 (20.6)
Chronic kidney disease	22 (13.8)
Chronic liver disease	4 (2.5)
Chronic lung disease	16 (10.0)
No comorbidity	55 (34.4)
≥1 comorbidity	105 (65.6)
SOFA score	5.15 (2.73); 5 (3.75–7); 0–14
CAC/Weston score	4.03 (3.32); 3 (1–7); 0–12
CAC burden group 0–4	99 (61.9)
CAC burden group 5–8	41 (25.6)
CAC burden group 9–12	20 (12.5)

Data are presented as mean (SD); median (IQR); or n (%).
CAC: coronary artery calcium; SOFA = Sequential Organ Failure Assessment

Table 2. Pearson correlations between CAC and SOFA scores

Subgroup	n	r	P
Overall	160	.260	.001
Male	92	.230	.03
Female	68	.139	.26
Hospitalization <10 d	104	.297	.002
Hospitalization ≥10 d	56	.031	.82
No comorbidity	55	.402	.002
≥1 comorbidity	105	.087	.38
Age <60 y	68	.173	.16
Age ≥60 y	92	.069	.51
CAC 0–4	99	.067	.51
CAC 5–8	41	−.031	.85
CAC 9–12	20	−.379	.10

CAC: coronary artery calcium; SOFA: Sequential Organ Failure Assessment
r=Pearson correlation coefficient
P values are two-sided. The Weston score was used for CAC quantification.

Table 3. Mean SOFA scores by CAC burden category in mechanically ventilated patients with COVID-19

CAC Burden Category	n	Mean (SD) SOFA Score
0–4	99	4.63 (2.58)
5–8	41	6.02 (2.61)
9–12	20	5.95 (3.15)

ANOVA. $F_{2,157}$=5.029; P=.008
Tukey Post Hoc Comparisons. The 5–8 group had a significantly higher mean SOFA score than the 0–4 group (mean difference, 1.398; adjusted P=.01). The comparisons of 9–12 vs 0–4 (mean difference, 1.324; adjusted P=.11) and 9–12 vs 5–8 (mean difference, −0.074; adjusted P=.99) were not statistically significant.
CAC: coronary artery calcium; SOFA: Sequential Organ Failure Assessment
CAC burden categories correspond to CAC/Weston scores of 0–4, 5–8, and 9–12.

Table 4. Multivariable linear regression analysis of factors associated with the SOFA score
The multivariable linear regression model included the CAC/Weston score, age, sex, hypertension, diabetes, dyslipidemia, chronic kidney disease, chronic liver disease, and chronic lung disease as predictors of the SOFA score. Results are reported as unstandardized coefficients (B), 95% CIs, and P values.

Variable	Coefficient (B)	95% CI	*P*
CAC/Weston score	0.009	−0.147 to 0.165	.91
Age, y	0.043	0.010 to 0.075	.01
Sex (female)	−0.489	−1.368 to 0.390	.28
Hypertension	0.014	−0.798 to 0.825	.98
Diabetes	0.344	−0.603 to 1.290	.47
Dyslipidemia	−0.840	−1.929 to 0.248	.13
Chronic kidney disease	2.648	1.390 to 3.907	<.001
Chronic liver disease	0.686	−1.824 to 3.195	.60
Chronic lung disease	0.896	−0.499 to 2.292	.21

Model Summary. Adjusted R^2=0.218; constant=2.774 (P=.02)
CAC: coronary artery calcium; SOFA: Sequential Organ Failure Assessment
Sex and comorbidity variables use binary indicator coding.

Discussion

In this retrospective analysis of mechanically ventilated patients with COVID-19, we observed a statistically significant positive, albeit modest, correlation between CAC burden (Weston score) and SOFA score–based MODS in the overall cohort (r=.260; P=.001). Be that as it may, this association did not persist after multivariable adjustment; in the final regression model, CAC burden was not independently associated with SOFA score (β=0.009; P=.91). Instead, age (β=0.043; P=.01) and chronic kidney disease (β=2.648; P<.001) emerged as the sole independent correlates of SOFA score in this cohort. Taken together, these findings suggest that CAC may reflect, rather than independently drive, the systemic vulnerability underlying disease severity, and should be interpreted only as an exploratory marker in this setting.

Mechanistic Insights: The Vascular-Systemic Link

The bivariate relationship between CAC and higher SOFA scores observed in the overall unadjusted analysis (r=.260; P=.001), as well as in

specific subgroup analyses, may be explained by a multifaceted pathophysiological link. We propose that CAC serves not only as a marker of coronary artery disease but also as a surrogate of systemic vascular health that may inform the host response to acute stress. Several biological mechanisms could plausibly explain the unadjusted association observed in this study; however, these mechanisms were not directly evaluated in our dataset.

First, patients with a higher CAC burden typically exhibit increased arterial stiffness and reduced vascular compliance. Under the physiologic stress of mechanical ventilation-often complicated by positive end-expiratory pressure-these patients possess a compromised "vascular reserve."[24,25] This reduced ability to accommodate shifts in cardiac output and systemic perfusion may contribute to end-organ hypoperfusion, which could adversely influence SOFA components, particularly the renal and hepatic domains.

Second, CAC is a marker of diffuse endothelial injury and systemic atherosclerosis. SARS-CoV-2 targets the vascular endothelium through ACE2 receptors, potentially inducing an exaggerated inflammatory response in patients with pre-existing atherosclerotic disease.[26,27] This synergy between chronic vascular damage and acute cytokine-mediated endotheliitis may contribute to the development of MODS.[28,29] Moreover, because CAC is frequently accompanied by microvascular disease, patients with severe CAC may be more susceptible to microvascular thrombosis, a recognized complication of COVID-19, leading to global microcirculatory failure.[30,31]

Importantly, these mechanistic considerations remain hypothesis-generating. The attenuation of the CAC–SOFA association after multivariable adjustment (β=0.009; P=.91) suggests that shared risk factors-particularly age (P=.01) and chronic kidney disease (P<.001)-partly account for the crude correlations, and that CAC may function as an indicator rather than an independent causal determinant of disease severity.

Explaining the Observed Correlation in Patients without Comorbidities

An exploratory subgroup finding was the stronger correlation between CAC and SOFA scores in patients without underlying diseases (r=.402; P=.002). Additionally, significant correlations were noted in male patients (r=.230; P=.03) and those with a shorter hospital stay (r=.297; P=.002). In patients with multiple comorbidities, organ involvement is often multifactorial, which may obscure the relationship between any single vascular marker and organ dysfunction. Conversely, in patients without diagnosed chronic illnesses, the presence of significant CAC may serve as a proxy for "hidden" vascular aging and subclinical atherosclerosis.[32] Nonetheless, because the independent association did not survive multivariable adjustment (P=.91), these subgroup observations should be considered exploratory and interpreted cautiously.

Clinical Implications and Imaging Strategy

The present findings partially corroborate previous reports suggesting that vascular calcification is a useful imaging marker in severity assessment.[32,33] Given the demand for rapid triage in the ICU, the visual semiquantitative grading of CAC on nongated chest CT provides an immediate, low-cost, and readily available biomarker at no additional radiation or acquisition cost.[16-22] While the Agatston score remains the reference standard, its requirement for ECG-gated acquisition makes it technically unfeasible in critically ill, mechanically ventilated patients.[16,29]

In this context, the Weston score offers a pragmatic semiquantitative approach for estimating CAC extent on nongated chest CT. Although it is not interchangeable with the Agatston score, previous studies have reported an association between Weston-based visual assessment and quantitative CAC measurements. Consistent with prior reports, CAC assessment may be reasonably integrated into routine chest CT reporting for ICU-admitted patients as a rapid adjunctive marker. Nevertheless, our multivariable findings indicate that CAC should be interpreted alongside established clinical predictors-particularly age and renal function-rather than as an isolated prognostic parameter.

Limitations

Several limitations merit consideration. First, the retrospective, single-center design and the

modest sample size limit generalizability. Second, the association between CAC and SOFA did not persist after multivariable adjustment, indicating that residual confounding or collinearity with age and renal disease cannot be excluded. Third, our one-way ANOVA showed significant differences in mean SOFA scores across CAC categories (P=.008), yet post hoc analysis demonstrated that this was driven solely by the comparison between the moderate and mild groups, indicating that the relationship is not strictly linear across all severity levels. Fourth, subgroup analyses were exploratory and not adjusted for multiple comparisons. The relatively small number of events or observations for some comorbid conditions, particularly chronic liver disease, may have limited the stability and precision of the multivariable estimates. Finally, the Weston score is a semiquantitative measure; although strongly correlated with Agatston scoring, it may not capture the full extent of calcification.

Conclusion

In mechanically ventilated patients with COVID-19, CAC burden showed a significant unadjusted positive correlation with SOFA score in the overall cohort (r=.260; P=.001), with notable exploratory associations in specific subgroups; however, it was not independently associated with SOFA score after multivariable adjustment for age, sex, and comorbidities (β=0.009; P=.91). Age (β=0.043; P=.01) and chronic kidney disease (β=2.648; P<.001) were the principal independent correlates of SOFA score in this cohort. CAC assessment on nongated chest CT may provide contextual information regarding underlying vascular disease, but it should not be interpreted as an isolated marker of organ dysfunction severity. Larger prospective multicenter studies are needed to determine its incremental clinical value.

Declarations:

Ethical Approval

This study received approval from the Ethics Committee of Zahedan University of Medical Sciences (IR.ZAUMS.REC.1402.354). Because of the retrospective, observational nature of the research, the institutional review board waived the requirement for informed consent from the patients.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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