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# Relationship between pre-existing cardiovascular disease and death and cardiovascular outcomes in critically ill patients with COVID-19

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## Abstract

**Background:** Pre-existing cardiovascular disease (CVD) is perceived as a risk factor for poor outcomes in patients with COVID-19. We sought to determine whether CVD is associated with in-hospital death and cardiovascular events in critically ill patients with COVID-19.

**Methods:** This study used data from a multicenter cohort of adults with laboratory confirmed COVID-19 admitted to intensive care units (ICUs) at 68 centers across the United States from March 1-July 1, 2020. The primary exposure was CVD, defined as pre-existing coronary artery disease, congestive heart failure, or atrial fibrillation/flutter. Myocardial injury on ICU admission defined as a troponin I or T level above the 99$^{th}$ percentile upper reference limit of normal was a secondary exposure. The primary outcome was 28-day in-hospital mortality. Secondary outcomes included cardiovascular events (cardiac arrest, new-onset arrhythmias, new-onset heart failure, myocarditis, pericarditis, or stroke) within 14 days.

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Supplemental Materials:

Tables S1–S12

Figures S1–S4

**Results:** Among 5,133 patients (3,231 male [62.9%]; mean age 61 years [standard deviation 15]), 1,174 (22.9%) had pre-existing CVD. A total of 1,178 (34.6%) died and 920 (17.9%) had a CV event. After adjusting for age, sex, race, body mass index, history of smoking, and comorbidities, pre-existing CVD was associated with a 1.15 (95% CI: 0.98–1.34) higher odds of death. No independent association was observed between pre-existing CVD and CV events. Myocardial injury on ICU admission was associated with higher odds of death (adjusted odds ratio [aOR]=1.93, 95%CI [1.61–2.31]) and CV events (aOR=1.82, 95%CI [1.47–2.24]), regardless of the presence of CVD.

**Conclusions:** CVD risk factors, rather than CVD itself, were the major contributors of outcomes in critically ill patients with COVID-19. The occurrence of myocardial injury, regardless of CVD, and its association with outcomes suggests it is likely due to multi-organ injury related to acute inflammation rather than exacerbation of preexisting CVD.

**Clinical Trial Registration:** NCT04343898; https://clinicaltrials.gov/ct2/show/NCT04343898

### Keywords

cardiovascular disease; COVID-19; risk factors; death; myocardial injury; troponin; inflammation

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a global pandemic as of March 2020 by the World Health Organization. Since March 2020, there have been nearly 90 million cases and over 1 million deaths attributed to COVID-19 in the United States alone.[1] The overall case fatality rate of COVID-19 is 1.8% in the United States, with estimates much higher for patients admitted to intensive care units (ICUs) and those with pre-existing conditions, such as cardiovascular disease (CVD).[2, 3]

COVID-19 is recognized as a hyper-inflammatory syndrome with aberrant immune activation and fulminant cytokine release resulting in multi-organ dysfunction, including adverse effects on the heart.[4] The relationship between COVID-19 and CVD is complex. Pre-existing CVD is common in patients hospitalized for COVID-19.[5] Additionally, COVID-19 has also been linked to cardiovascular complications, such as myocardial injury or infarction, myocarditis, heart failure, arrhythmias, and stroke, even in patients without a history of CVD.[6] Accordingly, patients with pre-existing CVD may be at a higher risk of poor in-hospital outcomes related to COVID-19, including death and cardiovascular complications.[7–9]

Prior studies examining the relationship between CVD and adverse outcomes in patients with COVID-19 were limited by being single center, having small sample sizes, or relying on billing codes and administrative databases lacking in data granularity, and thus were unable to comprehensively account for potential confounders.[10–15] Further, many studies were focused on patient populations outside the United States with highly differing risk factor profiles, or defined patients based on SARS-CoV-2 positivity rather than a clinical diagnosis of COVID-19, which could result in selection bias.[12, 16–18]

We performed a comprehensive analysis of the relationship between CVD and outcomes in severe COVID-19 through leveraging the Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 (STOP-COVID); a large multicenter cohort study of critically ill adults hospitalized for COVID-19 across the United States.

## METHODS

### Data availability

Due to restrictions on patient privacy and data sharing, data from STOP-COVID is not available for purposes of reproducing the results or replicating the procedure. Syntax and output files of statistical analyses can be made available upon reasonable request by contacting the corresponding author.

### Study Population & Design

STOP-COVID is a multicenter observational cohort study that enrolled 5,133 adult patients (≥18 years of age) with laboratory-confirmed COVID-19 admitted to ICUs at 68 hospitals across the United States.[9, 19–27] Patients were admitted to ICUs between March 1 and July 1, 2020, and were followed until the first of hospital discharge, death, or September 1, 2020. The study was approved by the institutional review boards at each participating site under a waiver of informed consent. Additional details regarding STOP-COVID are reported elsewhere.[9, 19–27] A list and map of participating sites are shown in Table S1 and Figure S1 in the Supplemental Material.

### Data Collection & Procedures

Medical records were reviewed by study personnel at each participating site and data were entered into REDCap, a secure, HIPAA-compliant web-based application. A standardized electronic case report form was used to ensure consistent data collection across sites. A variety of relevant patient data were collected from medical records, including demographics, coexisting conditions, home medications, physiologic data, and daily data on laboratory values and outcomes during the first 14 days after ICU admission. All data were validated using a series of automated verifications and were manually reviewed to assess for potential errors or incongruent values.[9]

### Exposure and Outcome Definitions

**Exposures—**The primary exposure was pre-existing CVD defined as a history of coronary artery disease (CAD), congestive heart failure (CHF), atrial fibrillation, or atrial flutter based on diagnoses documented in the medical record prior to or at the time of admission. CHF included patients with or without reduced left ventricular ejection fraction.

We explored myocardial injury as a secondary exposure. Myocardial injury at ICU admission was defined as a troponin I or T level above the 99$^{th}$ percentile upper reference limit of normal (URL) reported at each site (Table S2) and measured within 24-hours of ICU admission. If more than one troponin value was measured in this 24-hour period, the first value was recorded. We also assessed myocardial injury by grouping troponin levels according to multiples of the 99$^{th}$ percentile of the URL as follows: 1–2x, 2–3x, 3–4x, and

> 4x the URL. Lastly, we examined the change in troponin defined as the absolute fold change between the maximum and minimum troponin concentrations during hospitalization. All troponin measurements were recorded up to 14 days after ICU admission.

**Outcomes—**The primary outcome was in-hospital death within 28 days of ICU admission. Patients discharged alive prior to 28 days were considered alive at 28 days, an assumption that we validated in the original STOP-COVID report by contacting a subset of patients by phone after they were discharged.[9] The secondary outcome was a composite endpoint of cardiovascular (CV) events (cardiac arrest, new-onset arrhythmias, new-onset heart failure, myocarditis, pericarditis, or stroke) occurring within 14 days following ICU admission. New-onset arrhythmias were further stratified as ventricular fibrillation or sustained ventricular tachycardia, non-sustained ventricular tachycardia, and atrial fibrillation or flutter. Patients with pre-existing atrial fibrillation or flutter (n=187) were excluded from analyses of incident atrial fibrillation or flutter.

## Statistical Analysis

Clinical characteristics are reported as means and standard deviation for normally distributed continuous variables, medians and interquartile range (IQR) for non-normally distributed continuous variables, and frequencies and proportions for categorical variables. Group comparisons were made using t-tests, Wilcoxon rank-sum test, or chi-square tests for normal continuous, non-normal continuous, and categorical variables, respectively. To determine whether pre-existing CVD was independently associated with higher levels of thrombo-inflammation markers, we used linear regression models with C-reactive protein and D-dimer levels as the dependent variables, and CVD, age, race/ethnicity, smoking status, diabetes mellitus, hypertension, and chronic kidney disease as independent variables.

**Pre-Existing CVD, Myocardial Injury, and Outcomes—**We used multivariable logistic regression models to investigate the relationship between exposures and outcomes (death and CV events at 28 and 14 days, respectively). The following exposures were examined in separate models: (1) CVD vs. no CVD; (2) myocardial injury vs. no myocardial injury; (3) myocardial injury categorized as troponin level on ICU admission 1–2x, 2–3x, 3–4x, and >4x the URL vs. no myocardial injury; and (4) absolute fold change in troponin levels >URL categorized as <1.29-fold change, 1.3–9.3-fold change%, and >9.3-fold change (tertiles), with troponin levels in the normal range as the reference.

We created stepwise models with each outcome as the dependent variable. Model 0 was unadjusted; model 1 included the following demographic covariates: age group (18–39, 40–49, 50–59, 60–69, 70–79, ≥80 years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, other), and sex; model 2 included model 1 covariates in addition to the following cardiac risk factors: body-mass index (BMI; < 25, 25–29.9, 30–34.9, 35–39.9, ≥ 40 kg/m$^2$), smoking status (current, former, never), diabetes mellitus, hypertension, and chronic kidney disease (CKD); model 3 included model 2 covariates in addition to the modified Sequential Organ Failure Assessment (SOFA) score, a measure of illness severity calculated on ICU admission.[22, 28] Models 2 and 3 included adjustment for pre-existing CVD when myocardial injury is the exposure. We repeated the modeling

separately for patients with CAD vs. CHF to investigate their independent association with outcomes. In sensitivity analyses, we assessed whether treatment with remdesivir or corticosteroids impacted the association between pre-existing CVD and outcomes. To explore the possibility of competing events, we examined associations between pre-existing CVD,myocardial injury and the composite outcome of in-hospital death and cardiovascular events within 14 days. We further accounted for hospital-level differences by conducting a generalized linear mixed-effects model with a random effect for institution. Given that troponin is often only measured in high-risk patients or those with presenting symptoms, we conducted an analysis in which patients with missing troponin levels were assumed to have normal troponin. Lastly, we examined the interaction term myocardial injury*CVD to assess whether the association between myocardial injury and outcomes differed according to CVD status.

We computed the relative importance of clinical characteristics in their association with the outcomes based on the Gini index using a random forest approach.[29] To assess the contribution of CVD to outcomes, we computed the area under the curves (AUC) for models with clinical characteristics (model 2) with and without CVD and compared them using the Delong test.

For multivariable models, we used complete case analysis. A two-sided P-value < 0.05 was used to determine statistical significance. All analyses were performed using R Version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

### Characteristics of the Study Cohort

Of the 5,133 patients included in STOP-COVID, 1,174 (22.9%) had pre-existing CVD with a mean (SD) age of 61 (15) years. Of those with CVD, 492 (41.9%) had CAD without CHF, and 521 (44.4%) had CHF. Compared to those without CVD, patients with CVD were older (mean age 69 vs. 58) and more likely to have a smoking history (54.4% vs. 39.9%) and co-morbid conditions (hypertension [85% vs. 55%], diabetes mellitus [56% vs. 38%], CKD [20% vs. 9%]) (Table 1). Patients with CVD were also more likely to have higher serum creatinine on arrival to the ICU compared to those without CVD. Pre-existing CVD was not independently associated with higher C-reactive protein or D-dimer levels on ICU admission after adjusting for clinical characteristics (Table S3). Among those with CVD, patients with CHF were more likely to be women, non-Hispanic Black, have a history of atrial fibrillation or flutter and CKD, and be prescribed a mineralocorticoid receptor antagonist compared to those with CAD alone (Table 1).

### Incidence of Primary and Secondary Outcomes Stratified by Pre-Existing CVD

A total of 1,778 (34.6%) patients died within 28 days of ICU admission, and 920 (17.9%) experienced a cardiovascular event within 14 days following ICU admission. Compared to patients without CVD, those with CVD had a higher incidence of 28-day mortality (45.4% vs. 31.4%; P<0.001) and CV events (21.0% vs. 17.0%; P=0.002) (Table 1). Among patients

with CVD, the incidence of death was similar in patients with CAD compared to those with CHF (47.2% and 43.6%).

### Associations Between CVD and Death and Cardiovascular Events

Pre-existing CVD was associated with higher odds of 28-day mortality in both unadjusted models (model 0) and models adjusted for age, sex, and race (model 1) (adjusted odds ratio [aOR]=1.28 [95%CI: 1.11–1.48]). The association was attenuated after adjusting for comorbidities (model 2) and modified SOFA score (model 3) (aOR=1.15 [95%CI: 0.98–1.34]) (Figure 1). Similarly, whereas pre-existing CVD had been associated with higher odds of CV events in unadjusted analyses, it was no longer significant in multivariable models (aOR=0.95 [95%CI: 0.79–1.14]) (Figure 1 and Table S4). Trends were similar when examining the association between CAD and CHF individually with outcomes (Figure 1 and Table S4). These associations did not differ according to treatment with corticosteroids or remdesivir (Table S5).Findings were consistent when examining the association between pre-existing CVD and a composite of in-hospital death and CV events within 14 days (Figure S2).

Based on a random forest approach, we identified the most important variables associated with 28-day mortality as age, BMI, race/ethnicity, history of smoking, hypertension, diabetes mellitus, male sex, and pre-existing CKD, CHF, atrial fibrillation or flutter, and CAD in descending order of importance. Age, BMI, race, and history of smoking also had the highest importance scores for CV events (Figure S3). The AUC for clinical characteristics in their association with 28-day mortality and CV events was 0.69 (95% CI: 0.67–0.70) and 0.63 (95% CI: 0.62–0.65) respectively. The addition of CVD to the model had minimal impact on the AUC of mortality (ΔAUC=0.001, P=0.27) and CV events (ΔAUC=0.000, P=0.76).

### Prevalence of Myocardial Injury at ICU Admission and Measures of Illness Severity

A total of 2,741 patients had at least one troponin measured within 24 hours of ICU admission. Compared to patients without troponin measured at ICU admission, patients who had troponin measured were older, had higher BMIs, and were more likely to have a history of smoking, hypertension, and chronic kidney disease as well as a higher cumulative incidence of 28-day mortality (35.8% vs 33.4%) and CV events (20.4% vs 15.1%) (Table S6). Of those with troponin levels, 1,263 (46.1%) had troponin values >URL, consistent with myocardial injury. Among patients with myocardial injury, 334 (26.4%), 211 (16.7%), 114 (9.0%), and 604 (47.8%) had troponin values 1–2x, 2–3x, 3–4x, and > 4x the URL, respectively. A total of 2,533 patients had at least two troponin measurements during hospitalization, with n=901 having levels below the URL, and n=1632 with at least 1 measure >URL.

Patients with myocardial injury were more likely to be mechanically ventilated and had higher SOFA scores, c-reactive protein, and creatinine levels on ICU admission compared to those without myocardial injury (Figure 2). Patients with CVD had a significantly higher prevalence of myocardial injury on ICU admission (66.6% vs. 39.2%; P<0.001). After adjusting for demographics and clinical characteristics, patients with pre-existing CVD had

1.67-fold higher odds (95% CI: 1.33–2.11]) of experiencing myocardial injury compared to patients without CVD (Table S7).

### Myocardial Injury and Death and Cardiovascular Events

Patients with myocardial injury at ICU admission compared to those without had a higher incidence of 28-day mortality (47.2% vs. 26.0%; P<0.001) and CV events (26.8% vs. 14.9%; P<0.001) (Table S8). New onset atrial fibrillation or flutter, new onset CHF, and myocarditis or pericarditis were each more common in patients with myocardial injury (Table S8).

The presence of myocardial injury on admission was associated with higher odds of both 28-day mortality and CV events. In fully adjusted models, the odds of 28-day mortality and cardiovascular events was 1.93-fold (95% CI: 1.61–2.31) and 1.88-fold (95% CI: 1.53–2.32) higher, respectively, compared to those without myocardial injury on admission (Figure S4). Troponin elevation and a greater absolute change in troponin during hospitalization were monotonically associated with higher odds of 28-day mortality and CV events (Figure 3). In fully adjusted models, patients in the highest troponin elevation category (>4x URL) had a 2.77-fold (95% CI: 2.22–3.45) and 3.00-fold (95% CI: 2.35–3.81) higher odds of death and CV events compared to those without myocardial injury (Figure 3, Table S9). Likewise, patients with an absolute fold change in troponin of greater than 9.3 had a 3.02-fold (95% CI: 2.31, 3.92) and 2.94-fold (95% CI: 2.19, 3.94) higher odds of death and CV events compared to patients who did not have elevated troponin during hospitalization (Figure 3). These associations were unchanged after accounting for institution or assuming normal troponin levels in patients with missing troponin (Table S10 & Table S11). Patients with myocardial injury were also at a higher odds of new onset atrial fibrillation or flutter, new-onset heart failure, and myocarditis or pericarditis (Table S4). Consistent findings were observed when examining a composite outcome of death and cardiovascular events within 14 days (Figure S2). In sensitivity analyses, the associations between myocardial injury and death were similar in those with vs. without pre-existing CVD (P interaction=0.31), CAD (P interaction=0.67), or CHF (P interaction=0.10). The association between myocardial injury and CV events was also similar in those with vs. without pre-existing CVD (P interaction=0.11), CAD (P interaction=0.43) or CHF (P interaction=0.06) (Table S12).

## DISCUSSION

In this multicenter cohort study of over 5,000 critically ill adult patients hospitalized for COVID-19 in the United States, nearly one fourth of patients had pre-existing CVD. Patients with CVD had a close to 30% higher age and sex adjusted 28-day mortality compared to those without CVD. The association was heavily attenuated when accounting for comorbidities, suggesting that CV risk factors rather than CVD (defined here by the presence of CAD, HF or atrial fibrillation) are the main contributors to in-hospital outcomes in patients with severe COVID-19. Indeed, age, BMI, smoking, hypertension, and diabetes mellitus were the most important contributors to mortality. Myocardial injury at ICU admission was common, occurring in nearly half of the patients with available troponin levels, and associated with measures of illness severity. We found a monotonic association

between myocardial injury with odds of death and CV events, which was not dependent on the presence of CVD. Overall, our findings support the characterization of severe COVID-19 as a pulmonary disease with multi-organ injury related to systemic inflammation. The occurrence of myocardial injury independently of the presence of CVD and its association with outcomes suggests it is a marker of the severity of the acute illness from COVID-19 rather than exacerbation of pre-existing disease.

CVD is an unsurprisingly common comorbidity among critically ill patients with COVID-19 given its relation to age and chronic inflammation. The reported prevalence of CVD in patients with COVID-19 varied widely (2.5 to 40%).[5, 10–12, 14, 15, 30–33] The large variability in estimates could reflect differences in sample sizes across studies (with many having fewer than 200 patients), geographic location, definitions of CVD, and COVID-19 severity. One large cohort study of 5,700 critically and non-critically ill patients hospitalized with COVID-19 in New York City reported that 11% of patients had a history of CAD and 6.9% had CHF.[5] These estimates were similar to those in our study despite the difference in severity of illness between cohorts, and suggests that CVD itself may not be a direct contributor to the severity of COVID-19 disease.

Studies reporting on the link between pre-existing CVD and COVID-19 related outcomes are conflicting.[34–39] Critical illness related to COVID-19 is thought to exacerbate pre-existing CVD by altering hemodynamics and the hypercoagulable milieu.[40] However, we did not find pre-existing CVD to be a major contributor to in-hospital mortality or CV events in patients with COVID-19 such as myopericarditis and arrhythmias independently of risk factors. Findings were similar when stratified between patients with CAD vs. CHF, in whom we would have expected outcomes would be worse. Circulating markers of acute inflammation were also not independently associated with pre-existing CVD. Conversely, hypertension and diabetes mellitus were much stronger predictors of mortality in COVID-19. However, findings should not be construed as implying patients with CVD are not at high risk as most have a high burden of risk factors for COVID-19 such as diabetes mellitus, hypertension, obesity, and smoking.[41]

Myocardial injury on ICU admission was common in this cohort, with estimates higher than those reported in prior studies of hospitalized patients with COVID-19, likely due to the current study being comprised of ICU patients only.[17, 30, 42, 43] The magnitude of myocardial injury correlates with COVID-19 disease severity and has been consistently associated with adverse outcomes across studies.[7, 12, 18, 42–46] In addition, a recent study found that hospitalized patients with COVID-19 who develop a ST-segment elevation myocardial infarction had higher rates of in-hospital mortality.[47] We found that a greater change in troponin values during hospitalization was associated with worse outcomes. The association between myocardial injury and death and CV events did not differ between patients with and without pre-existing CVD, supporting the notion that myocardial injury and CV events in COVID-19 are related to injury from mechanisms pertaining to the acute illness, such as endothelial dysfunction and a hypercoagulable state, rather than an exacerbation of pre-existing CVD.[18]

### Strengths and Limitations

STOP-COVID is the one of the largest and most comprehensive multicenter cohort studies of critically ill patients with COVID-19, which provided considerable statistical power and the ability to perform detailed multivariable adjustment in our analyses. Through its focus on critically ill patients, STOP-COVID allows us to identify the clinical relevance of pre-existing CVD and myocardial injury in the COVID-19 population at highest risk of death and CV events. There are several limitations to this analysis. The focus on ICU patients limits generalizability to the non-ICU COVID-19 population. Our definition of CVD was limited to the presence of CAD, CHF, or atrial fibrillation or flutter, and does not capture the full breadth of CVD. Pre-existing CVD and CV events were also determined based on documentation in the medical records rather than objective measures such as cardiac imaging or cardiac markers. Due to its observational nature, troponin levels were not measured systematically, lending a risk of selection bias. While we adjusted for demographics and clinical characteristics associated with whether a patient had troponin measured and severe outcomes, we acknowledge this will not fully account for the risk of bias. Due to different troponin assays across sites, we modeled the change in troponin during hospitalization as a relative fold-change. However, given patients with at least two troponin measurements were included in this analysis, survival bias is possible. We additionally adjusted for hospital-level characteristics, including institution, which did not change our findings. Findings regarding the association between troponin and outcomes are consistent with previous reports. Data on left ventricular ejection fraction were not available, precluding performing subgroup analyses differentiated CHF with and without left ventricular dysfunction. Additionally, because CV events were collected for only the first 14 days following ICU admission, their incidence is likely an underestimate. Based on prior data[9], we assumed patients discharged alive prior to 28 days were alive at 28 days, however it is possible that a subset of patients may have died after discharge and were unaccounted for in this analysis. Lastly, these data were collected prior to the implementation of the COVID-19 vaccine, thus it is unknown how the current trajectory of the COVID-19 pandemic would influence these findings.

## Conclusion

In summary, critically ill patients with COVID-19 and pre-existing CVD had higher mortality than those without CVD. However, CVD risk factors rather than CVD itself appear to be the most important contributors to outcomes. Myocardial injury was common and strongly associated with death and CV events regardless of underlying CVD status, reflecting the severity of the hyper-inflammatory phase of COVID-19. Patients with CVD should be construed as a high-risk patient group due to their burden of shared risk factors with severe COVID-19 outcomes such as hypertension, diabetes mellitus, obesity, and smoking. Studies on subpopulations with more severe underlying CVD, such as those with advanced heart failure or high-risk CAD, are warranted to further refine risk profiles in patients with COVID-19.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Non-standard Abbreviations and Acronyms

| | |
|---|---|
| **AUC** | area under curve |
| **BMI** | body mass index |
| **CAD** | coronary artery disease |
| **CV** | cardiovascular |
| **CHF** | congestive heart failure |
| **CKD** | chronic kidney disease |
| **COVID-19** | coronavirus disease 2019 |
| **CVD** | cardiovascular disease |
| **ICU** | intensive care unit |
| **IQR** | interquartile range |
| **SOFA** | Sequential Organ Failure Assessment |
| **STOP-COVID** | Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19 |
| **URL** | upper reference limit of normal |

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**What is known?**

- COVID-19 is a hyper-inflammatory syndrome resulting in multi-organ dysfunction, including the heart.
- Patients with pre-existing cardiovascular disease are perceived to be at higher risk of poor outcomes in COVID-19 based on small, single center studies.

**What this study adds?**

- This study includes data from one the largest and most comprehensive multicenter cohort studies of critically ill patients hospitalized for COVID-19.
- Cardiovascular risk factors, rather than pre-existing cardiovascular disease, were the main contributors to in-hospital in patients with severe COVID-19.
- Myocardial injury was strongly associated with death and cardiovascular events regardless of a history of cardiovascular disease and likely reflected the severity of the acute illness rather than exacerbation of pre-existing disease.

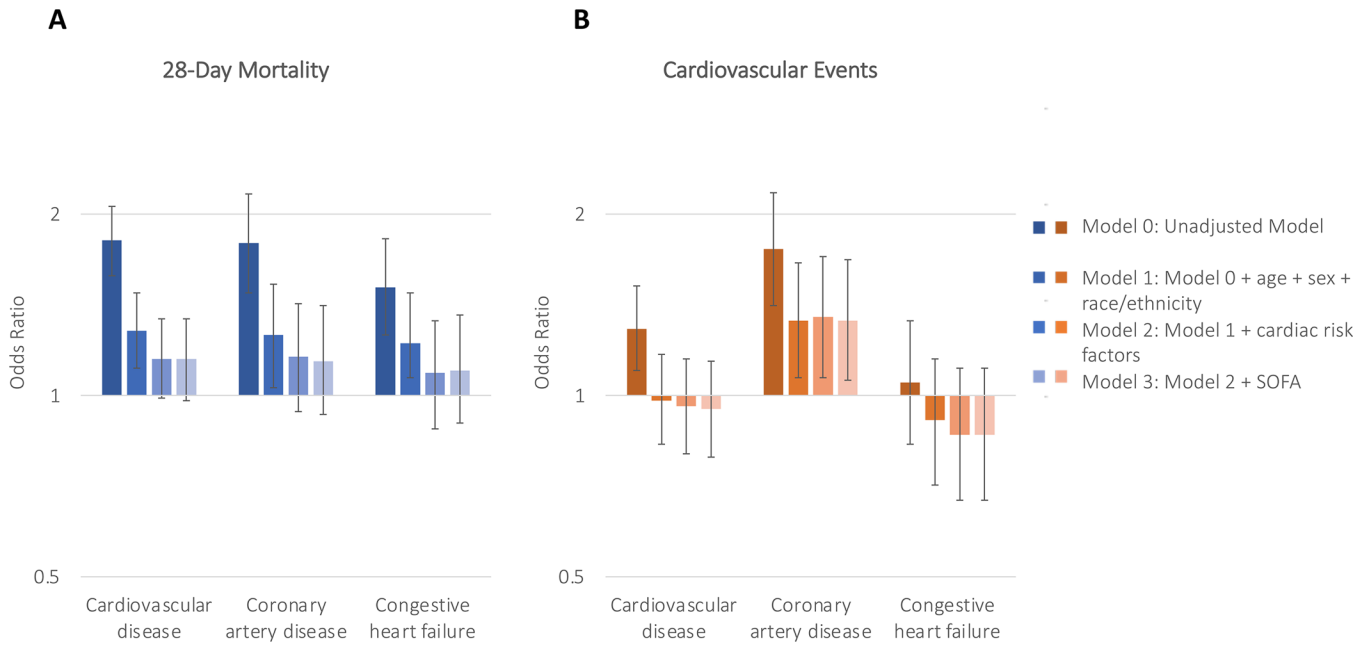


**Figure 1. Associations between cardiovascular disease, coronary artery disease, and congestive heart failure with 28-day mortality and cardiovascular events.**

Bar graphs depicting the odds ratio and 95% confidence intervals for 28-day mortality (Panel A) and cardiovascular events (Panel B) using four different models. Model 0 was unadjusted. Model 1 was adjusted for age, race/ethnicity, and sex. Model 2 incorporated model 1 in addition to body mass index, smoking status, and history of pre-existing diabetes mellitus, hypertension, and chronic kidney disease. Model 3 included the modified Sequential Organ Failure Assessment score. Based on model 3, neither cardiovascular disease, coronary artery disease, nor congestive heart failure were associated with 28-day mortality or cardiovascular events.

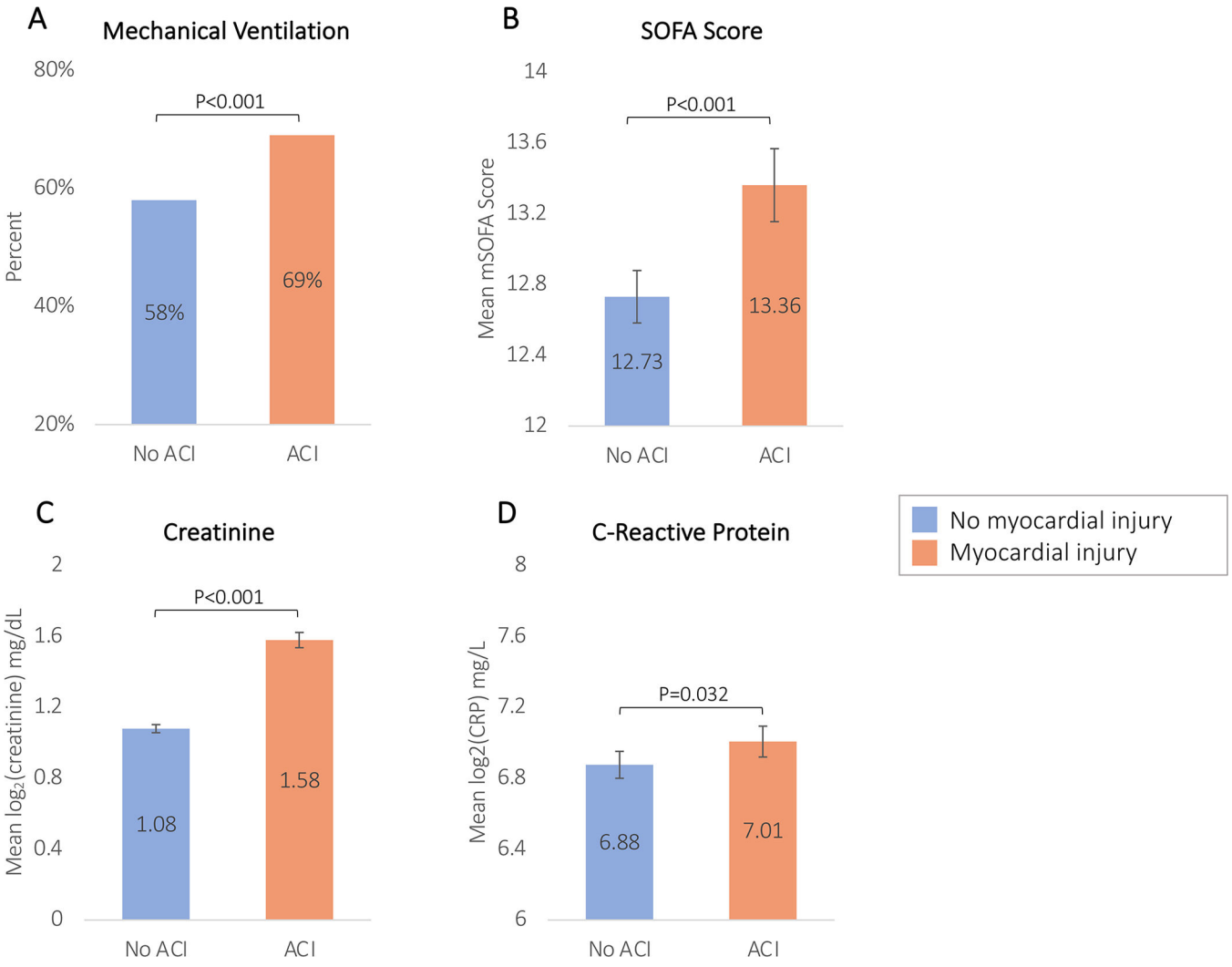


**Figure 2. Bar graphs comparing measures of COVID-19 illness severity by myocardial injury on admission for mechanical ventilation, modified SOFA score, creatinine, and c-reactive protein.**

Panel A displays the proportion of patients on mechanical ventilation at ICU admission. Panels B, C, and D compare the means of modified SOFA scores, creatinine, and c-reactive protein between patients with and without myocardial injury at ICU admission. Creatinine and c-reactive protein are $\log_2$ transformed. Abbreviations: ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

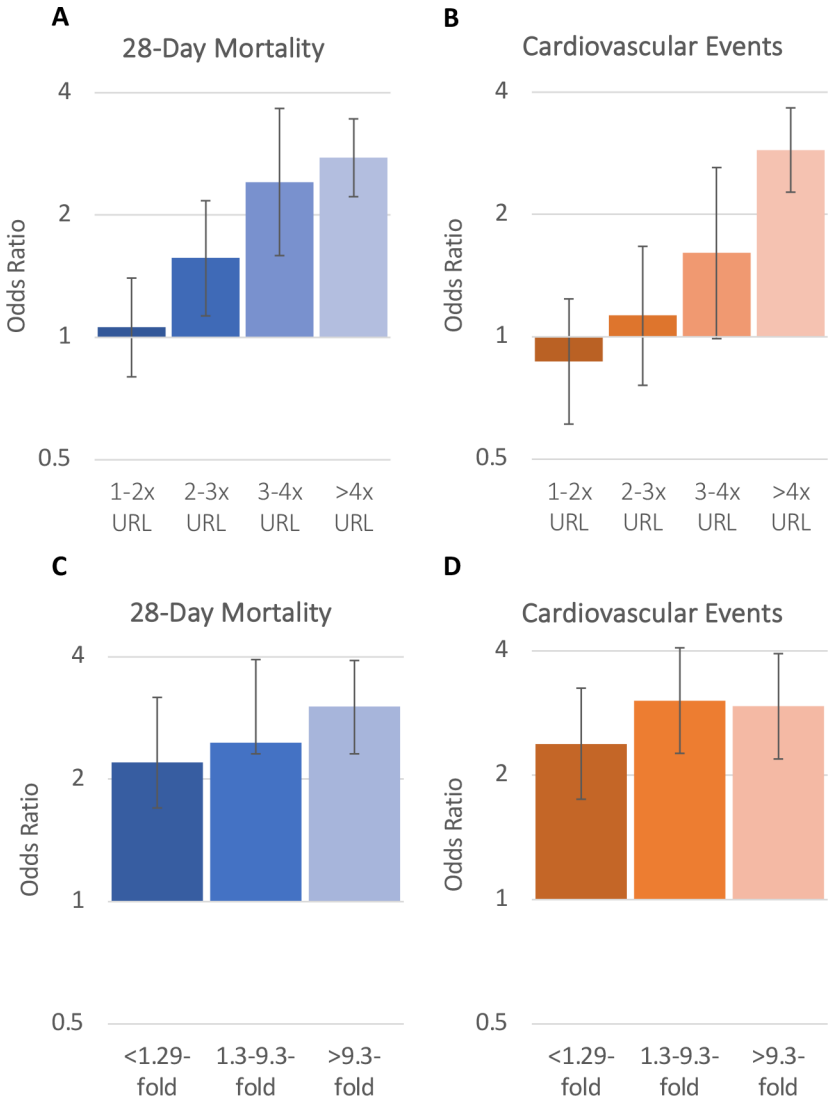


**Figure 3. Associations between troponin elevation on ICU admission and troponin fold change during hospitalization with 28-day mortality (A,C) and cardiovascular events (B,D).**

Bar graphs depicting the odds ratios and 95% confidence intervals for 28-day mortality (Panel A) and cardiovascular events (Panel B) based on acute cardiac injury on ICU admission categorized as troponin elevation 1–2x, 2–3x, 3–4x, and > 4x the URL vs. no acute cardiac injury (reference) based on model 3. Panels C and D depict odds ratios and 95% confidence intervals based on the absolute fold change in troponin during hospitalization categorized as an absolute fold change of <1.29, 1.3–9.3%, and >9.3% compared to patients with no elevated troponin measurements during hospitalization (reference) for 28-day mortality (Panel C) and cardiovascular events (Panel D) based on model 3. Abbreviations: ICU, intensive care unit; URL, upper reference limit of normal

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**Table 1.**

Demographics and clinical characteristics of STOP-COVID cohort

| | Overall cohort | | | Patients with cardiovascular disease | | |
|---|---|---|---|---|---|---|
| | **No cardiovascular disease (n=3,959)** | **Cardiovascular disease (n=1,174)** | **P-value** | **Coronary artery disease (n=492)** | **Congestive heart failure (n=521)** | **P-value** |
| **Demographics** | | | | | | |
| Age, years, mean (SD) | 59 (15) | 69 (12) | <0.001 | 69 (10) | 68 (13) | 0.009 |
| Male, n (%) | 2476 (62.5) | 755 (64.3) | 0.29 | 354 (72.0) | 291 (55.9) | <0.001 |
| Race/Ethnicity, n (%) | | | <0.001 | | | <0.001 |
| Hispanic/Latino | 1030 (26.0) | 166 (14.1) | | 78 (15.9) | 61 (11.7) | |
| Non-Hispanic Black | 1034 (26.1) | 369 (31.4) | | 129 (26.2) | 210 (40.3) | |
| Non-Hispanic White | 940 (23.7) | 397 (33.8) | | 169 (34.3) | 159 (30.5) | |
| Other | 955 (24.1) | 242 (20.6) | | 116 (23.6) | 91 (17.5) | |
| **Cardiac risk factors** | | | | | | |
| BMI, $kg/m^2$, mean (SD) * | 34 (22) | 33 (22) | 0.40 | 31 (16) | 34 (22) | 0.05 |
| Smoking Status, n (%) | | | <0.001 | | | 0.57 |
| Non-Smoker | 2379 (60.1) | 535 (45.6) | | 215 (43.7) | 239 (45.9) | |
| Former Smoker | 799 (20.2) | 448 (38.2) | | 203 (41.3) | 195 (37.4) | |
| Current Smoker | 189 (4.8) | 73 (6.2) | | 28 (5.7) | 37 (7.1) | |
| Coexisting conditions, n (%) | | | | | | |
| Hypertension | 2159 (54.5) | 995 (84.8) | <0.001 | 414 (84.1) | 453 (86.9) | 0.24 |
| Diabetes mellitus | 1511 (38.2) | 654 (55.7) | <0.001 | 291 (59.1) | 298 (57.2) | 0.57 |
| Atrial fibrillation or flutter | 0 (0.0) | 392 (33.4) | <0.001 | 62 (12.6) | 169 (32.4) | <0.001 |
| Chronic kidney disease | 356 (9.0) | 316 (26.9) | <0.001 | 111 (22.6) | 179 (34.4) | <0.001 |
| **Home medications, n (%)** | | | | | | |
| ACE-I/ARB | 1140 (28.8) | 556 (47.4) | <0.001 | 244 (49.6) | 256 (49.1) | 0.93 |
| MRA | 47 (1.2) | 72 (6.1) | <0.001 | 12 (2.4) | 55 (10.6) | 0.002 |
| Beta-blocker | 642 (16.2) | 721 (61.4) | <0.001 | 309 (62.8) | 318 (61.0) | 0.61 |
| Statin | 1167 (29.5) | 787 (67.0) | <0.001 | 373 (75.8) | 330 (63.3) | 0.001 |
| Aspirin | 589 (14.9) | 580 (49.4) | <0.001 | 302 (61.4) | 241 (46.3) | <0.001 |
| Anticoagulation | 170 (4.3) | 352 (30.0) | <0.001 | 91 (18.5) | 174 (33.4) | <0.001 |

| | Overall cohort | | | Patients with cardiovascular disease | | |
|---|---|---|---|---|---|---|
| | No cardiovascular disease (n=3,959) | Cardiovascular disease (n=1,174) | P-value | Coronary artery disease (n=492) | Congestive heart failure (n=521) | P-value |
| **Laboratory findings on ICU admission, median (IQR)** | | | | | | |
| Creatinine, mg/dL † | 1.0 (0.8, 1.5) | 1.4 (1, 2.6) | <0.001 | 1.3 (1, 2.3) | 1.7 (1.1, 3.1) | <0.001 |
| Hemoglobin, g/dL ‡ | 12.7 (11.2, 14.1) | 11.9 (10.1, 13.6) | <0.001 | 12.4 (10.8, 13.8) | 11.2 (9.5, 13.1) | <0.001 |
| Lactate, mmol/L § | 1.6 (1.1, 2.3) | 1.6 (1.1, 2.6) | 0.10 | 1.6 (1.1, 2.6) | 1.6 (1.1, 2.70) | 0.81 |
| C-reactive protein, mg/‖ | 151 (80, 233) | 133 (75, 218) | 0.007 | 138 (82, 219) | 124 (70, 202) | 0.09 |
| D-dimer, mg/L # | 1287 (647, 3690) | 1190 (653, 2555) | 0.08 | 1208 (689, 2820) | 1177 (551, 2220) | 0.11 |
| White blood cell count, /uL ** | 8.7 (6.2, 12) | 7.7 (5.6, 11.1) | <0.001 | 7.8 (5.5, 11.3) | 7.6 (5.5, 10.9) | 0.34 |
| Lymphocyte count, /uL †† | 10 (6, 15.3) | 10 (6.1, 15) | 0.95 | 9.4 (5.4, 15) | 10.9 (7.0, 15.4) | 0.048 |
| **Severity of illness on ICU admission, mean (SD)** | | | | | | |
| mSOFA score | 12.8 (3.2) | 13.4 (3.4) | <0.001 | 13.5 (3.2) | 13.4 (3.6) | 0.41 |
| **In-hospital treatment, n (%)** | | | | | | |
| Corticosteroids | 1491 (37.7) | 460 (39.2) | 0.35 | 206 (41.9) | 196 (37.6) | 0.19 |
| Remdesivir | 66 (1.7) | 17 (1.4) | 0.60 | 7 (1.4) | 5 (1.0) | 0.70 |
| **In-hospital outcomes, n (%)** | | | | | | |
| Death within 28 days | 1245 (31.4) | 533 (45.4) | <0.001 | 232 (47.2) | 227 (43.6) | 0.17 |
| Cardiovascular events within 14 days | 674 (17.0) | 246 (21.0) | 0.002 | - | - | - |
| Ventricular fibrillation or sustained VT | 65 (1.6) | 32 (2.7) | 0.023 | 12 (2.4) | 15 (2.9) | 0.81 |
| Non-sustained VT | 43 (1.1) | 38 (3.2) | <0.001 | 12 (2.4) | 19 (3.6) | 0.35 |
| Atrial fibrillation or flutter | 404 (10.2) | 126 (19.2) ‡‡ | <0.001 | 77 (17.9) ‖‖ | 49 (13.9) ## | <0.001 |
| New-onset heart failure | 123 (3.1) | 33 (5.3) §§ | <0.001 | 28 (5.8) *** | - | - |
| Myocarditis or pericarditis | 127 (3.2) | 49 (4.2) | 0.08 | 27 (5.5) | 19 (3.6) | 0.043 |
| Stroke | 37 (0.9) | 15 (1.3) | 0.39 | 6 (1.2) | 7 (1.3) | 0.99 |

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; ICU, intensive care unit; IQR = interquartile range; MRA, mineralocorticoid receptor; mSOFA, modified Sequential Organ Failure Assessment score; SD, standard deviation; VT, ventricular tachycardia

* Missing data for 200 patients (3.9%)

† Missing data for 286 patients (5.6%)

*Circ Cardiovasc Qual Outcomes*. Author manuscript; available in PMC 2023 October 04.

‡ Missing data for 328 patients (6.4%)

§ Missing data for 1961 patients (38.6%)

‖ Missing data for 1890 patients (37.0%)

# Missing data for 2263 patients (44.3%)

** Missing data for 332 patients (6.5%)

†† Missing data for 1037 patients (20.3%)

‡‡ Out of 656 patients without atrial fibrillation or flutter at admission

§§ Out of 624 patients without congestive heart failure at admission

‖‖ Out of 430 patients without atrial fibrillation or flutter at admission

## Out of 352 patients without atrial fibrillation or flutter at admission

*** Out of 468 patients without congestive heart failure at admission