Prevalence and Impact of Myocardial Injury in Patients Hospitalized with COVID-19 Infection

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Prevalence and Impact of Myocardial Injury in Patients Hospitalized with COVID-19 Infection

Brief title: Myocardial Injury in Patients Hospitalized with COVID-19

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ABSTRACT

Background: The degree of myocardial injury, as reflected by troponin elevation, and associated outcomes among US hospitalized patients with Coronavirus Disease 2019 (COVID-19) are unknown.

Objectives: To describe the degree of myocardial injury and associated outcomes in a large hospitalized cohort with laboratory-confirmed COVID-19.

Methods: Patients with COVID-19 admitted to one of five Mount Sinai Health System hospitals in New York City between February 27th and April 12th, 2020 with troponin-I (normal value <0.03ng/mL) measured within 24 hours of admission were included (n=2,736). Demographics, medical history, admission labs, and outcomes were captured from the hospitals' EHR.

Results: The median age was 66.4 years, with 59.6% men. Cardiovascular disease (CVD) including coronary artery disease, atrial fibrillation, and heart failure, was more prevalent in patients with higher troponin concentrations, as were hypertension and diabetes. A total of 506 (18.5%) patients died during hospitalization. In all, 985 (36%) patients had elevated troponin concentrations. After adjusting for disease severity and relevant clinical factors, even small amounts of myocardial injury (e.g. troponin I 0.03-0.09ng/mL, n=455, 16.6%) were significantly associated with death (adjusted HR: 1.75, 95% CI 1.37-2.24; P<0.001) while greater amounts (e.g. troponin I>0.09 ng/dL, n=530, 19.4%) were significantly associated with higher risk (adjusted HR 3.03, 95% CI 2.42-3.80; P<0.001).

Conclusions: Myocardial injury is prevalent among patients hospitalized with COVID-19 however troponin concentrations were generally present at low levels. Patients with CVD are more likely to have myocardial injury than patients without CVD. Troponin elevation among patients hospitalized with COVID-19 is associated with higher risk of mortality.

Condensed Abstract (100/100 words): Myocardial injury reflected as elevated troponin in Coronavirus Disease (COVID-19) is not well characterized among US patients. We describe the prevalence of myocardial injury and its impact on outcomes among hospitalized patients with confirmed COVID-19 who had troponin-I measurements within 24 hours of admission (N=2,736). Elevated troponin concentrations (normal <0.03ng/mL) were commonly observed in patients hospitalized with COVID-19, most often present at low levels, and associated with increased risk of death. Patients with cardiovascular disease (CVD) or CVD risk factors were more likely to have myocardial injury.

Key Words: Myocardial injury, Troponin, Coronavirus, COVID-19

Abbreviations:

ACE:	angiotensin-converting enzyme
ACEi:	angiotensin-converting enzyme inhibitor
AF:	atrial fibrillation
ARB:	angiotensin II receptor blocker
ARDS:	acute respiratory distress syndrome
CAD:	coronary artery disease
CKD:	chronic kidney disease
COPD:	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
CVD:	cardiovascular disease

DM:	diabetes mellitus
EHR:	electronic health records
HF:	heart failure
HTN:	hypertension
ICD 9/10:	International Classification of Disease, Revision 9/10
MSHS:	Mount Sinai Health System
SARS-CoV-2:	severe acute respiratory syndrome coronavirus-2

Introduction

Coronavirus Disease (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is now one of the deadliest pandemics in modern history. The mode of infection of COVID-19 is thought to be direct entry of the SARS-CoV-2 virus into cells via the human angiotensin-converting enzyme 2 (ACE2) receptor, which is expressed predominantly in the lungs but also throughout the cardiovascular system (1). Thus, while the most virulent manifestation of COVID-19 is acute respiratory distress syndrome (ARDS), reports from Europe and China have also demonstrated cardiac injury reflected through elevated troponin concentrations among infected patients (2–5). In these limited case series, troponin elevation was more common in patients with preexisting cardiovascular disease (CVD) and, when present, was associated with higher rates of adverse outcomes in patients hospitalized with COVID-19 (6). However, the observational nature and small sample sizes limit the generalizability of these findings. Additionally, there are no large studies from the United States (US), the current epicenter of the global pandemic.

As such, major gaps remain in our current understanding of the underlying mechanisms by which SARS-CoV-2 affects the cardiovascular system and how such involvement may alter clinical outcomes: First, the range of troponin elevation across different subpopulations based on history of CVD compared to those without history of CVD is unknown among patients in the US. Second, whether these troponin elevations represent primary myocardial infarction, supply-demand inequity, or non-ischemic myocardial injury remains unclear. Finally, the impact of myocardial injury in the context of COVID-19 infection on outcomes is not well studied. We sought to explore these aims amongst a large cohort of patients hospitalized with COVID-19 in New York City.

METHODS

Study Population

Patients in this study were drawn from five New York City hospitals comprising the Mount Sinai Health System (MSHS): Mount Sinai Hospital, in East Harlem; Mount Sinai West, in Midtown Manhattan; Mount Sinai St. Luke's, in Harlem; Mount Sinai Queens, in Astoria; and Mount Sinai Brooklyn, in the Midwood neighborhood of Brooklyn. We included all patients admitted to a MSHS hospital with a laboratory confirmed SARS-CoV-2 infection who were at least 18 years old and had a troponin measurement within the first 24 hours of admission between February 27th and April 12th, 2020. The Mount Sinai Institutional Review Board approved this research under a regulatory protocol allowing for analysis of patient-level COVID-19 data.

Data Collection

Data was collected from electronic health records (EHR) from the five hospitals. Variables collected included demographics, laboratory measurements, disease diagnoses, comorbidities, procedures, and outcomes (death, intubation, or hospital discharge). Comorbidities were extracted using International Classification of Disease (ICD) 9/10 billing codes for atrial fibrillation (AF), asthma, coronary artery disease (CAD), cancer, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes (DM), heart failure (HF), and hypertension (HTN). Troponin I concentrations were assessed via the Abbott Architect method (Abbott, Abbott Park, Illinois) wherein the 99th percentile for a normal population is 0.028 ng/mL. The reference level for normal in MSHS is less than 0.03 ng/mL. We computed the CURB-65 score for patients at admission to adjust for illness severity on presentation (7). Blood Urea Nitrogen (BUN), respiratory rate, systolic and diastolic blood pressures, and age

components of the CURB-65 scoring system were available as structured fields, whereas "confusion" was abstracted using natural language processing of presenting emergency department notes by using the Clinithink engine to encode all identifiable SNOMED concepts and query for positive instances of symptoms related to 'Mentally alert' (SNOMED: 248234008) or 'Oriented' (SNOMED: 247663003) (8). Patients without either term were classified as having confusion when determining CURB-65 risk strata. Body mass index (BMI) was not available for 219 patients (8.0%). We imputed these BMI values using multiple imputation by chained equations with predictive means matching. Further details of the imputation process are provided in the **Supplemental Appendix (Supplemental Figure 1)**.

Statistical Analysis

Descriptive analyses were performed by troponin levels stratified into normal (0.00-0.03 ng/mL), mildly elevated (between one and three times the upper limit of normal, or >0.03-0.09 ng/mL), and elevated (more than three times the upper limit of normal, or >0.09 ng/mL). Categorical variables were reported as total count and percentage of patients. Continuous non-troponin laboratory values were reported as median and interquartile range. We used troponin measurements within 24 hours of admission. If multiple troponin measurements were available within 24 hours, the patient's first measurement was used. We performed ANOVA to assess for heterogeneity in admission troponin levels across the five hospitals included in the present study.

To assess the effects of troponin levels on outcomes, we conducted a survival analysis with the dependent variable of time to mortality, setting time zero to time of hospital admission. Patients were considered to be right-censored if they were (1) discharged from the hospital alive or (2) remained in the hospital at the time of data freeze (Midnight, April 12th). We fit Cox proportional hazards regression models with mortality as the dependent variable, adjusting for

age, sex, BMI, race, ethnicity, history of CAD, history of AF, history of HF, history of HTN, history of CKD, history of DM, statin use, angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) use, and CURB-65 score at hospital admission. Age was modeled as age at time of admission, while gender and history of CAD, AF, HTN, CKD, DM, statin, and ACE/ARB usage were modeled with binary variables. . BMI was modeled as a continuous variable. CURB-65 is an integer score ranging from zero to five representing illness severity. Self-declared race was included in the model with indicator variables corresponding to Caucasian, African American, Asian, Pacific Islander, Other, or Unknown with Caucasian as the reference level. Self-declared ethnicity was included in models as Hispanic/Latino, Non-Hispanic/Latino, and Unknown with Hispanic/Latino as the reference level. We tested for deviations from the proportional hazards assumption by plotting Martingale residuals from the Cox proportional hazards model vs. linearized predictions. 95% confidence intervals from a LOESS best-fit line fit to the Martingale residuals included 0 for all values of the linear predictions, visually indicating there was not significant deviation from the proportional hazards assumption. We then plotted Kaplan-Meier curves for survival stratified by troponin group.

In addition to the study's primary outcome of mortality, we conducted a secondary analysis examining a composite outcome composed of mortality or intubation with mechanical ventilation. For patients who were intubated and then subsequently died, time to intubation was used. We then conducted a Cox proportional hazards regression analysis controlling for the same covariates as in the primary analysis. Finally, to understand general trends in subsequent troponin values after admission for the subset of patients who had more than one troponin measurement, we fit patient-level linear regression models to each patient’s troponin levels as a function of time from initial troponin measurement and split patients into strata based upon the

slope of the regression coefficient into those whose troponin levels on average increased or decreased. We then fit Cox proportional hazards regression models to these strata with the dependent variable of time until mortality, again controlling for the same baseline variables. All analyses were conducted in R version 3.6.1. Survival curve and cumulative incidence visualizations were produced with the survminer R package (7, 8).

As a sensitivity analysis, we conducted a complementary analysis where discharge from the hospital was considered to be a competing risk since mortality status could not be assessed after hospital discharge. We used the cmprsk R package for this analysis (9). Hazard ratios for the troponin variables from this analysis were not meaningfully different from our standard survival analysis.

RESULTS

Patient Characteristics and Troponin Levels

During the study period, 3,069 COVID-19 positive patients were hospitalized at one of five MSHS New York City hospitals. Of these, 2,736 (89.1%) had at least one troponin-I measurement within 24 hours of admission. The median age was 66.4 years, 40.7% of patients were over age 70, and 59.6% were male. One-quarter of all patients self-identified as African American and 27.6% self-identified as Hispanic or Latino. The mean BMI was 29.8 kg/m2 ± 6. A history of CVD, including CAD, AF, or HF, was present in 35% of patients. Altogether, risk factors for CVD of DM or HTN, were present in 65% of the cohort. Accordingly, 22% were receiving ACE inhibitors or ARBs, and 36% were receiving statins. CURB-65 scores to represent illness severity displayed increasing trends by troponin strata: patients with troponin levels of 0-0.03 ng/mL exhibited a mean (SD) CURB-65 score of only 0.90 (0.95), whereas patients with troponin levels 0.03-0.09 were found to have scores of 1.76 (1.02) and those with

troponin levels of >0.09 ng/mL exhibited scores of 2.01 (1.05) ($p<0.001$). (**Table 1**). Baseline characteristics and outcomes for the 323 (11.8%) patients who did not have troponin measurements assessed within 24 hours of admission are shown in Supplemental Table 1. Patients who did not have troponins measured were more likely to be female (55.1% vs. 40.4%, $\chi 2$ $p<0.001$), were younger (55.0 years vs. 66.4 years, t-test $p<0.001$), and had lower rates of medical comorbidities (atrial fibrillation, asthma, CAD, cancer, CKD, COPD, diabetes, HF, and HTN, all $p<0.05$, 2-proportion Z test with Benjamini-Hochberg Correction for multiple hypothesis testing).

Admission troponin-I concentrations are presented in **Figure 1**. Notably, 1751 (64%) patients had an initial troponin within the normal range. Few patients (86 patients, 3.1%) had an admission troponin over 1 ng/mL within 24 hours of admission, while 173 (6.3%) had a troponin elevation over 1 ng/mL at any point during their hospital stay. Patient characteristics as well as admission vital signs and laboratory measurements, stratified by admission troponin-I, are also displayed in **Table 1**. Troponin elevations were categorized as mildly elevated and elevated as previously defined. Higher troponin concentrations were seen in patients who were over the age of 70. Mean presentation troponin levels varied moderately across the five hospital sites, ranging from 0.10±0.40 to 0.36±2.54 (One-way ANOVA, $F=2.32$, $df=5$, $p=0.04$) (Supplemental Figure 2). However, linear regression revealed that the hospital site explained only 0.4% of the variance in presenting troponin levels ($R2=0.004$).

The proportion of patients with CVD (defined here as CAD, AF, or HF) increased with higher troponin concentrations. Specifically, in those patients with more significant myocardial injury (troponin I>0.09ng/mL), CVD including CAD, AF, and HF, was more prevalent (34.9%, 13.0%, and 25.3% respectively) compared to patients with mildly elevated troponins (21.3%,

10.1% and 14.7% respectively) and those with normal troponins (9.8%, 5.2%, and 4.3% respectively). **Figure 2** plots troponin measurements within 24 hours of admission among patients with CVD. Individuals with CVD generally presented with higher initial troponins than those without CVD. Similar trends for myocardial injury were seen in patients with history of HTN, DM, and CKD, but not in those with a history of asthma or cancer. Patient characteristics stratified by history of CVD, risk factors, and no history of either are shown in **Table 2.** ACEi and ARB use as well as statin use were more prevalent amongst increasing troponin strata. They were also more prevalent when stratified by presence of risk factors of CVD and presence of CVD.

Acute phase and inflammatory markers were higher among patients with more substantial troponin elevations as well. In particular, median D-dimer, C-reactive protein, lactate dehydrogenase, and procalcitonin were higher in patients with elevated initial troponins (2.54 ug/mL, 149.9 mg/L, 520.0 U/L, 0.81 ng/mL respectively) than those with mildly elevated troponins (1.65 ug/mL, 136.78 mg/L, 456.0 U/L, 0.30 ng/mL respectively) and those with normal troponins (1.17 ug/mL, 114.25 mg/L, 425.0 U/L, 0.15 ng/mL respectively). Patients who had lower hemoglobin, hypo- or hypertension, or tachycardia generally presented with higher troponins than those who did not. In analyzing trends in troponin concentrations over time, we found that 922 patients (33.7%) displayed an increase in troponin concentration after the first 24 hours while 811(29.6%) saw a decrease during hospitalization. The remaining 1003 (36.7%) did not have further troponin values available for analysis. Of those with increasing troponins over time, 223 (24%) died, compared to 102 (13%) of those with decreasing troponins and 181 (18%) of those with no subsequent troponin measurements. The hazard ratio for mortality in those with an increasing troponin trend compared to those with a decreasing troponin trend was 2.13 (95% CI: 1.68-2.70, $p<0.001$) after adjusting for age, gender, race, ethnicity,BMI, CAD, DM, HF, hHTN, AF,, atrial

chronic kidney disease, CURB-65 score, ACE-inhibitor or ARB use, and statin use (Supplemental Figure 3).

Outcomes

Mortality

Of 2736 COVID-19 patients included in our study, 506 (18.5%) died, 1132 (41.4%) were discharged, and 1098 (40.1%) remained hospitalized at the time of data freeze for this report. The median length of stay was 5.75 days (Q1-Q3: 3.36-9.56). In a Cox proportional hazards regression model, increased age, BMI and higher illness severity (as indicated by higher CURB-65 scores) were associated with increased risk of death while gender, race/ethnicity and risk factors for CVD and CVD (CAD, AF, HF) were not (Table 3). Statin use but not ACE inhibitor or ARB use was associated with improved survival (HR 0.57, 95% CI 0.47, 0.69).

Figure 3 presents cumulative incidence plots displaying probability for three possible outcomes (mortality, discharge from hospital, or continued hospitalization) over time. Milder forms of myocardial injury (e.g. troponin concentration 0.03-0.09 ng/mL) were associated with less frequent discharge and higher risk of death than troponin levels in the reference range after adjustment for clinically relevant covariates (adjusted HR: 1.75, 95% CI 1.37-2.24) (**Figure 4A).** Troponin concentrations over 0.09 ng/dL were associated with more pronounced risk of death (adjusted HR 3.03, 95% CI 2.42-3.80) after adjustment. This risk was consistent across patients stratified by history of CVD, CVD risk factors such as DM or HTN only, and neither CVD nor risk factors. **(Figure 4B**). A sensitivity analysis using a competing-risks framework demonstrated similar adjusted hazards ratios for risk of death – HR 2.02 (95% CI: 1.58-2.60) for troponin concentrations >0.03-0.09 ng/mL, and HR 3.52 (95% CI: 2.79-4.45) for troponin concentrations >0.09 ng/mL (Supplemental Table 2).

Composite Outcome of Mortality or Mechanical Ventilation

Altogether, 813 of 2,746 patients (29.6%) either died or underwent intubation by the end of the period of observation, compared to the 506 patients who died in the primary analysis (18.4%). In a Cox proportional hazards regression analysis controlling for the same covariates as in the primary analysis, troponin elevation remained a significant predictor of outcomes. We observed an HR 1.75 (95% CI: 1.44-2.13, p<0.001) for troponin concentrations >0.03-0.09 ng/mL, and an HR of 2.97 (95% CI: 2.47-3.56) for troponin concentrations >0.09 ng/mL. A Kaplan-Meier plot demonstrating the trends in composite outcome by troponin strata is provided in Supplemental Figure 4.

DISCUSSION

Although pulmonary manifestations are its most common consequence, COVID-19 causes systemic inflammation with varying presentations of cardiac involvement as well (10). In this multihospital retrospective cohort study of nearly 3000 patients, we demonstrate the following observations: 1) Myocardial injury is common among patients hospitalized with COVID-19 but is more often mild, associated with low-level elevation in troponin concentration. 2) More significant myocardial injury may be associated with more than a tripling in risk of mortality. 3) COVID-19 patients with a history of CVD are more likely to suffer myocardial injury than patients without CVD but without obvious corroborating evidence for primary acute myocardial infarction (**Central Illustration**).

Though troponin elevation above the 99th percentile of the upper reference limit (URL) is considered the central marker of “myocardial injury” (11), underlying pathophysiologic mechanisms must be elucidated according to clinical circumstances. Myocardial injury is best recognized in the context of ischemia, however several non-ischemic mediated mechanisms,

which include apoptosis, myocardial strain, myocyte necrosis, and increased cell membrane permeability mediated exocytotic release of troponin may contribute to such injury (12, 13). , According to the Fourth Universal Definition of Myocardial Infarction, very few patients met strict criteria for acute myocardial infarction. Though some patients in this cohort certainly suffered ischemic myocardial damage from either Type 1 or 2 myocardial infarction, it is possible that a majority of injury observed was mediated through a non-coronary mechanism. Challenges exist regarding understanding underlying etiology however.

Despite several reports of COVID-19 associated myocarditis, to date, no case has demonstrated COVID-19 genome in cardiac tissue on biopsy or autopsy accompanied by troponin elevation consistent with criteria used to diagnose myocarditis (3–5, 14–16). Other postulated mechanisms by which COVID-19 leads to cardiovascular morbidity include direct myocardial injury as a result of the inflammatory cascade or cytokine release, microvascular damage due to disseminated intravascular coagulation and thrombosis, direct entry of SARS-CoV-2 into myocardial cells via binding to ACE2 receptors, hypoxemia combined with increased metabolic demands of acute illness leading to myocardial injury akin to Type 2 Myocardial Infarction, and finally acute coronary syndrome from acute inflammation-triggered destabilization of atheromas (17–19).

In a recent case series of 18 patients with COVID-19 infection and ST-segment elevation on electrocardiogram, 10 were deemed to have non-coronary myocardial injury by virtue of non-obstructive disease on coronary angiography and/or normal wall motion on echocardiography (20). Despite lower troponin concentrations in this group, nine died as opposed to 4/8 in the ST-Elevation MI group, which may suggest higher mortality associated with non-ischemic mediated myocardial injury in the setting of COVID-19, however more data are needed.

We demonstrate that myocardial injury was prevalent among a large hospitalized cohort in the US, occurring in 36%. Evidence for myocardial injury was more frequent in our cohort compared to recent reports from China (2, 21–24). These prior studies included between 41 and 416 patients and noted prevalence of myocardial injury ranging from 7-28%. Similar to these smaller reports, we also noted that patients with myocardial injury tended to be older and have a history of CVD. We also noted lower hemoglobin values, higher inflammatory markers, and more frequent rates of tachycardia or hypo/hypertension.

Because SARS-CoV-2 enters cells via binding to the ACE2 receptor, previous concerns existed as to increased risk of adverse outcomes conferred by ACE inhibitors or ARBs; these worries have been somewhat dissipated in light of recent studies showing no increased risk associated with use of these drugs (25,26). We demonstrate a protective association with statin use but no association with ACE inhibitors or ARBs, consistent with a simultaneous report by Reynolds et.al. The benefit of statins in the setting of myocardial injury is well established (27–29), yet whether statins confer an antiinflammatory effect or allow for amelioration of endothelial dysfunction in COVID-19 have not been elucidated. It is also possible that statin use in-hospital is confounded by physicians' treatment priorities, as statins may simply be discontinued for patients who are intubated or otherwise became critically ill. Given the impressive effect size we observed in this study (HR=0.57), it may be that at least some component of statins' observed efficacy is due to this confounding phenomenon. Interestingly, higher BMI was associated with increased mortality in the setting of COVID-19 among our cohort, consistent with a prior report (30). This may be a reflection of the high prevalence of DM and concomitant metabolic syndrome in our population, although BMI did not differ by troponin

strata or the presence of risk factors for CVD or CVD. Data on insulin resistance and cholesterol were not available in our cohort.

Although present as low-level concentrations, troponin elevation to greater than 3 times the URL was associated with a three-fold increased risk of mortality despite adjustment for clinically relevant factors. This finding is in keeping with a report from Wuhan, China of 416 patients by Shi et al, which demonstrated a hazard ratio of 3.41 [95% CI, 1.62-7.16] for death in patients with myocardial injury as compared to patients without. Guo and colleagues reported similar findings among 187 patients also in Wuhan but emphasized that although myocardial injury was more prevalent in patients with history of CVD, outcomes were more favorable in patients with CVD and no myocardial injury as compared to individuals with myocardial injury and no history of CVD. We similarly show that myocardial injury when present, regardless of history of CVD or risk factors, was associated with worse outcomes inclusive of mechanical intubation or mortality.

Limitations

There are some notable limitations of the present analysis. First, there are limitations inherent to the use of EHR for patient level data in such a large sample size not explicitly verified by manual chart review. For example, sample size did not permit manual review of electrocardiogram findings to correlate with troponin elevations. Despite these limitations, the use of EHR enabled timely analysis and rapid dissemination of crucial information in a large patient cohort at the epicenter of the global pandemic. Second, some patients included had not completed their hospital course at the time of data freeze. We accounted for this by conducting a secondary, complementary survival analysis where hospital discharge was treated as a competing risk as outlined in the Methods section. Results from our competing risks analysis were not

meaningfully different from a standard survival analysis where discharged patients were simply considered to be right-censored. Use of anticoagulation and antiviral therapy was not included in part due to patient participation in clinical trials leading to incomplete data. Further, natriuretic peptide levels were not available for more than two-thirds of the study cohort within 24 hours of admission and therefore patterns in the context of myocardial injury could not be described. Outcomes analyses were focused upon troponin measurements made at hospital admission and less upon serial troponin measurements obtained over the course of each patient's hospital stay, although we also demonstrate that trends in troponin levels over time are associated with mortality. Troponin concentrations were not available in 323 patients who had fewer comorbidities than the 2,736 patients for whom troponin tests were ordered, and as such may have impacted our results. Finally it was not possible to ascertain mechanisms of death including cardiovascular and non-cardiovascular causes.

CONCLUSION

Myocardial injury is prevalent, generally at low levels, among patients with acute COVID-19 and is associated with worse outcomes. History of CVD was associated with myocardial injury in the setting of COVID-19 infection. These results suggest abnormal troponin concentrations on admission may be helpful with regard to triage decision-making. However, whether treatment strategies based on troponin concentrations would be expected to improve outcomes remains a testable hypothesis.

Perspectives

Competency in Medical Knowledge: Myocardial injury, reflected by troponin elevation, is common among patients hospitalized with COVID-19, particularly among those with a history of cardiovascular disease, and is associated with a high risk of mortality.

Translational Outlook: Further research is needed to elucidate the mechanisms responsible for myocardial injury in patients with COVID-19 and compare clinical outcomes associated with ischemic vs. non-ischemic types.

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Figure Legends

Figure 1. Distribution of maximum in-hospital troponin values for all patients with maximum troponin values below 1.0 ng/mL. Patients with troponin concentrations greater than 1.0 ng/mL are not shown.

Figure 2. Plot of longitudinal troponin values over time, stratified by history of cardiovascular disease (CAD, HF, AFib) or no history of cardiovascular disease. Smoothing lines fit via LOESS regression with shaded areas indicating 95% confidence intervals.

Figure 3. Cumulative incidence plots displaying probability for three possible outcomes (mortality, discharge from hospital, or continued hospitalization) over time.

Figure 4a. Kaplan-Meier plot for survival past hospital admission, stratified by troponin grouping. Patients were considered to be right-censored if they were discharged alive from the hospital or were still hospitalized at the time of data freeze (April 12, 2020). Survival times were significantly different between groups ($p<0.001$). **Figure 4b.** Hazard ratios and 95% confidence intervals calculated by Cox proportional hazards regression models for mortality stratified by comorbidities. Patients with cardiovascular disease had comorbidities of coronary artery disease, heart failure, or atrial fibrillation. Patients with cardiovascular risk factors had comorbidities of DM or HTN, but not cardiovascular disease.

Central Illustration. Myocardial injury reflected by troponin concentrations above the upper reference limit (URL) of 0.03ng/mL was present in 36%of patients hospitalized with COVID-19. Troponin levels among patients hospitalized with COVID-19 were generally under 1.0 ng/mL. Even small amounts of myocardial injury (e.g. troponin I 0.03-0.09ng/mL, n=455, 16.6%) were associated with death (adjusted HR: 1.77, 95% CI 1.39-2.26; $P<0.001$) while greater amounts (e.g. troponin I>0.09 ng/dL, n=530, 19.4%) were associated with more pronounced risk for death

(adjusted HR 3.23, 95% CI 2.59-4.02). Troponin elevation in the setting of acute COVID-19 may primarily reflect non-ischemic or secondary myocardial injury.

Table 1. Baseline characteristics of admitted patients, stratified by troponin concentration.

COVID-19 Patient Characteristics Stratified by Troponin Levels, N = 2736					
	All Patients	Troponin I (ng/mL)			
Variable		**0-0.03**	**0.03-0.09**	**>0.09**	**P Value**
Patient N	2736	1751	455	530	
Sex (Female)	1106 (40.4)	721 (41.2)	173 (38.0)	212 (40.0)	0.463
Race (%)					<0.001
White	634 (23.2)	377 (41.2)	116 (25.5)	141 (26.6)	
African American	700 (25.6)	398 (22.7)	141 (31.0)	161 (30.4)	
Asian	105 (3.8)	74 (4.2)	15 (3.3)	16 (3.0)	
Pacific Islander	29 (1.1)	19 (1.1)	6 (1.3)	4 (0.8)	
Other	1157 (42.3)	806 (46.0)	163 (35.8)	188 (35.5)	
Unknown Race	111 (4.1)	77 (4.4)	14 (3.1)	20 (3.8)	
Ethnicity (%)					0.001
Hispanic/Latino	762 (27.9)	547 (31.2)	107 (23.5)	108 (20.4)	

Non-Hispanic/Latino	1622 (59.3)	979 (55.9)	294 (64.6)	349 (65.8)	
Unknown Ethnicity	352 (12.9)	225 (12.8)	54 (11.9)	73 (13.8)	
Age (%)					<0.001
(18,30]	49 (1.8)	46 (2.6)	2 (0.4)	1 (0.2)	
(30,40]	161 (5.9)	146 (8.3)	3 (0.7)	12 (2.3)	
(40,50]	248 (9.1)	209 (11.9)	21 (4.6)	18 (3.4)	
(50,60]	470 (17.2)	357 (20.4)	62 (13.6)	51 (9.6)	
(60,70]	694 (25.4)	474 (27.1)	114 (25.1)	106 (20.0)	
(70,80]	596 (21.8)	337 (19.2)	117 (25.7)	142 (26.8)	
(80,90]	400 (14.6)	153 (8.7)	104 (22.9)	143 (27.0)	
(90,100]	117 (4.3)	29 (1.7)	32 (7.0)	56 (10.6)	
Clinical Covariates					
Body Mass Index (mean (SD))	29.8 (6.5)	30.07 (6.46)	29.16 (6.44)	29.08 (6.51)	0.002
ACEi or ARB Use (%)	601 (22.0)	332 (19.0)	118 (25.9)	151 (28.5)	<0.001
Statin Use (%)	984 (36.0)	516 (29.5)	223 (49.0)	245 (46.2)	<0.001
CURB-65 Score (mean (SD))	1.26 (1.10)	0.90 (0.95)	1.76 (1.02)	2.01 (1.05)	
Comorbidities					

Atrial fibrillation (N (%))	206 (7.5)	91 (5.2)	46 (10.1)	69 (13.0)	<0.001
Asthma (N (%))	229 (8.4)	154 (8.8)	36 (7.9)	39 (7.4)	0.537
Coronary artery disease (N (%))	453 (16.6)	171 (9.8)	97 (21.3)	185 (34.9)	<0.001
History of cancer (N (%))	195 (7.1)	123 (7.0)	38 (8.4)	34 (6.4)	0.481
Chronic kidney disease (N (%))	273 (10.0)	90 (5.1)	66 (14.5)	117 (22.1)	<0.001
COPD (N (%))	158 (5.8)	70 (4.0)	39 (8.6)	49 (9.2)	<0.001
Diabetes (N (%))	719 (26.3)	378 (21.6)	153 (33.6)	188 (35.5)	<0.001
Heart Failure (N (%))	276 (10.1)	75 (4.3)	67 (14.7)	134 (25.3)	<0.001
Hypertension (N (%))	1065 (38.9)	595 (34.0)	205 (45.1)	265 (50.0)	<0.001
Laboratory Values					
Hemoglobin (median [IQR])	12.70 [11.30, 13.90]	12.90 [11.70, 14.00]	12.60 [11.20, 13.90]	11.90 [10.20, 13.40]	<0.001
Lymphocyte (%) (median [IQR])	13.20 [8.12, 20.30]	14.90 [9.10, 21.87]	11.20 [7.10, 18.45]	9.70 [6.20, 14.60]	<0.001
D-dimer (median [IQR])	1.43 [0.79, 2.75]	1.17 [0.71, 2.15]	1.65 [1.05, 3.21]	2.54 [1.51, 4.93]	<0.001
D-dimer above 1 mcg/mL (N (%))	1453 (66.2)	846 (58.5)	282 (76.4)	325 (85.8)	<0.001
C-reactive protein (median [IQR])	126.69 [63.71, 214.20]	114.25 [56.61, 194.80]	136.78 [72.30, 228.95]	149.94 [95.09, 246.65]	<0.001
Creatine kinase (median [IQR])	177.50	136.00	336.00	332.00	<0.001

	[83.25, 502.50]	[72.50, 326.75]	[120.00, 981.50]	[155.00, 1015.00]	
Lactate dehydrogenase (median [IQR])	441.00	425.00	456.00	520.00	<0.001
	[332.00, 592.00]	[325.00, 551.00]	[339.50, 616.75]	[368.00, 753.50]	
Ferritin (median (IQR))	780.50	724.00	828.00	1093.00	<0.001
	[376.00, 1899.00]	[350.8, 1629.8]	[378.00, 1858.50]	[488.00, 2696.00]	
Procalcitonin (median [IQR])	0.21 [0.09, 0.69]	0.15 [0.07, 0.38]	0.30 [0.12, 0.80]	0.81 [0.28, 2.59]	<0.001
Creatinine (median [IQR])	0.98 [0.75, 1.58]	0.85 [0.70, 1.12]	1.25 [0.90, 2.08]	2.09 [1.24, 4.48]	<0.001
Prothrombin time (pt) (median [IQR])	14.30 [13.50, 15.60]	14.00 [13.30, 14.90]	14.40 [13.80, 16.48]	15.20 [14.10, 16.80]	<0.001
Partial thromboplastin time (aPTT)	32.90 [29.52, 37.90]	32.30 [29.40, 36.80]	33.00 [29.70, 38.98]	34.40 [30.10, 40.70]	0.002
(median [IQR])					
Albumin (median [IQR])	3.00 [2.60, 3.30]	3.00 [2.70, 3.30]	2.90 [2.50, 3.20]	2.90 [2.50, 3.20]	<0.001
Bilirubin (Total) (median [IQR])	0.60 [0.40, 0.80]	0.60 [0.40, 0.80]	0.60 [0.40, 0.80]	0.60 [0.40, 0.90]	0.048
Sodium (median [IQR])	138.00	137.00	138.00	139.00	<0.001
	[135.00, 141.00]	[135.00, 140.00]	[135.00, 141.00]	[136.00, 144.00]	
Tachycardia (HR > 100 BPM) (N (%))	647 (23.6)	393 (22.4)	95 (20.9)	159 (30.0)	<0.001
Fever (>38.0°C) (N (%))	517 (18.9)	372 (21.3)	67 (14.8)	78 (14.8)	<0.001
Hypotension (SBP < 100 mmHg) (N (%))	228 (8.3)	123 (7.0)	40 (8.8)	65 (12.3)	0.001

SBP above 160 mmHg (N (%))	227 (8.3)	104 (5.9)	53 (11.7)	70 (13.2)	<0.001

Table 2. Baseline characteristics of admitted patients stratified by history of cardiovascular disease, cardiovascular risk factors, or neither.

COVID-19 Patient Characteristics					
Stratified by History of Cardiovascular Disease or Risk Factors, N = 2736					
		Cardiovascular Disease History			
Variable	All Patients	**No Risk Factors**	**Risk Factors**	**Cardiovascular Disease**	**P Value**
Patient N	2736	1374	706	656	
Sex (Female)	1106 (40.4)	521 (37.9)	309 (43.8)	276 (42.1)	0.022
Age (mean (SD))	66.40 (15.80)	61.54 (16.72)	65.74 (13.75)	72.98 (12.81)	<0.001
Race (%)					<0.001
White	634 (23.2)	316 (23.0)	130 (18.4)	188 (28.7)	
African American	700 (25.6)	323 (23.5)	201 (28.5)	176 (26.8)	
Asian	105 (3.8)	48 (3.5)	28 (4.0)	29 (4.4)	
Pacific Islander	29 (1.1)	8 (0.6)	12 (1.7)	9 (1.4)	
Other	1157 (42.3)	602 (43.8)	318 (45.0)	237 (36.1)	

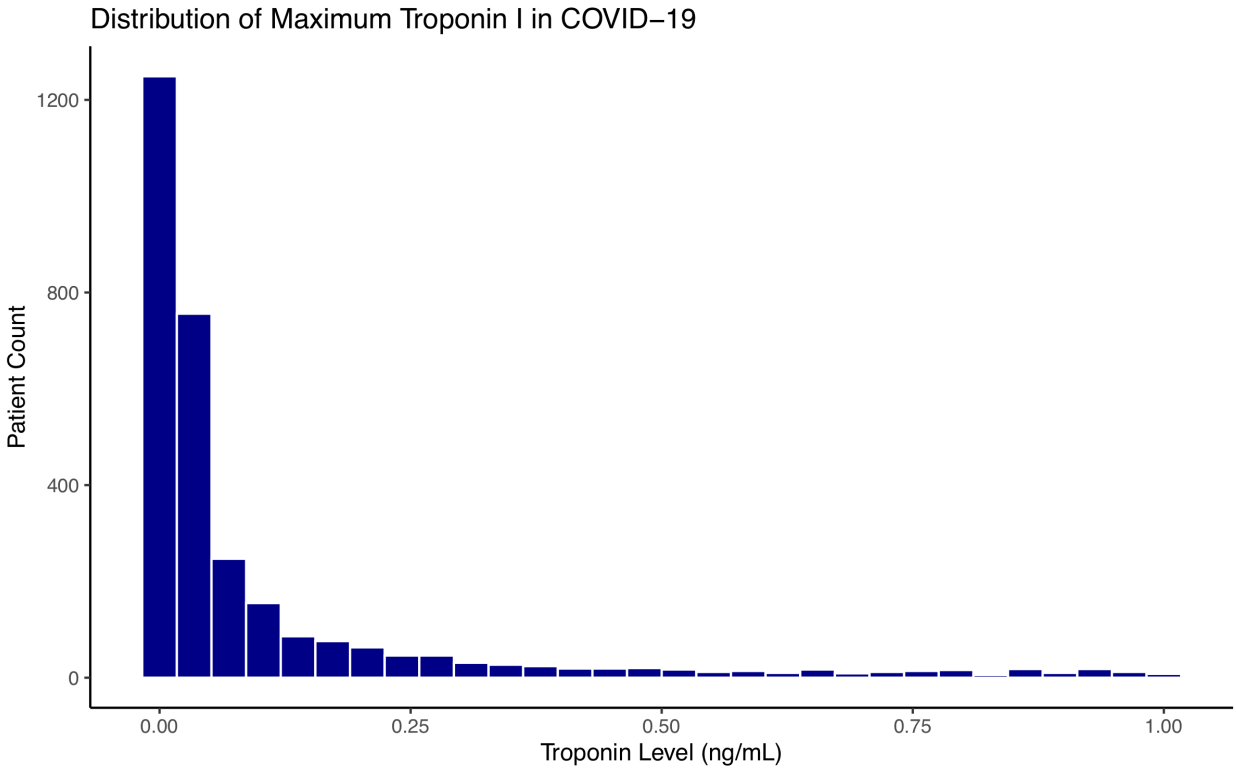
Unknown Race	111 (4.1)	77 (5.6)	17 (2.4)	17 (2.6)	
Ethnicity (%)					0.001
Hispanic/Latino	762 (27.9)	389 (28.3)	214 (30.3)	159 (24.2)	
Non-Hispanic/Latino	1622 (59.3)	789 (57.4)	401 (56.8)	432 (65.9)	
Unknown Ethnicity	352 (12.9)	196 (14.3)	91 (12.9)	65 (9.9)	
Clinical Covariates					
Body Mass Index (mean (SD))	29.8 (6.5)	29.90 (6.51)	30.40 (6.66)	29.90 (6.51)	0.001
ACEi or ARB Use (%)	601 (22.0)	130 (9.5)	211 (29.9)	260 (39.6)	<0.001
Statin Use (%)	984 (36.0)	278 (20.2)	312 (44.2)	394 (60.1)	<0.001
CURB-65 Score (mean (SD))	1.26 (1.10)	1.00 (1.07)	1.29 (1.04)	1.77 (1.03)	<0.001
Laboratory Values					
Hemoglobin (median [IQR])	12.70 [11.30, 13.90]	13.00 [11.80, 14.0]	12.40 [11.00, 13.80]	12.30 [10.47, 13.50]	<0.001
Lymphocyte (%) (median [IQR])	13.20 [8.12, 20.30]	13.10 [8.10, 20.10]	13.90 [8.50, 21.20]	12.90 [7.68, 19.72]	0.133
D-dimer (median [IQR])	1.43	1.29	1.51	1.64	<0.001

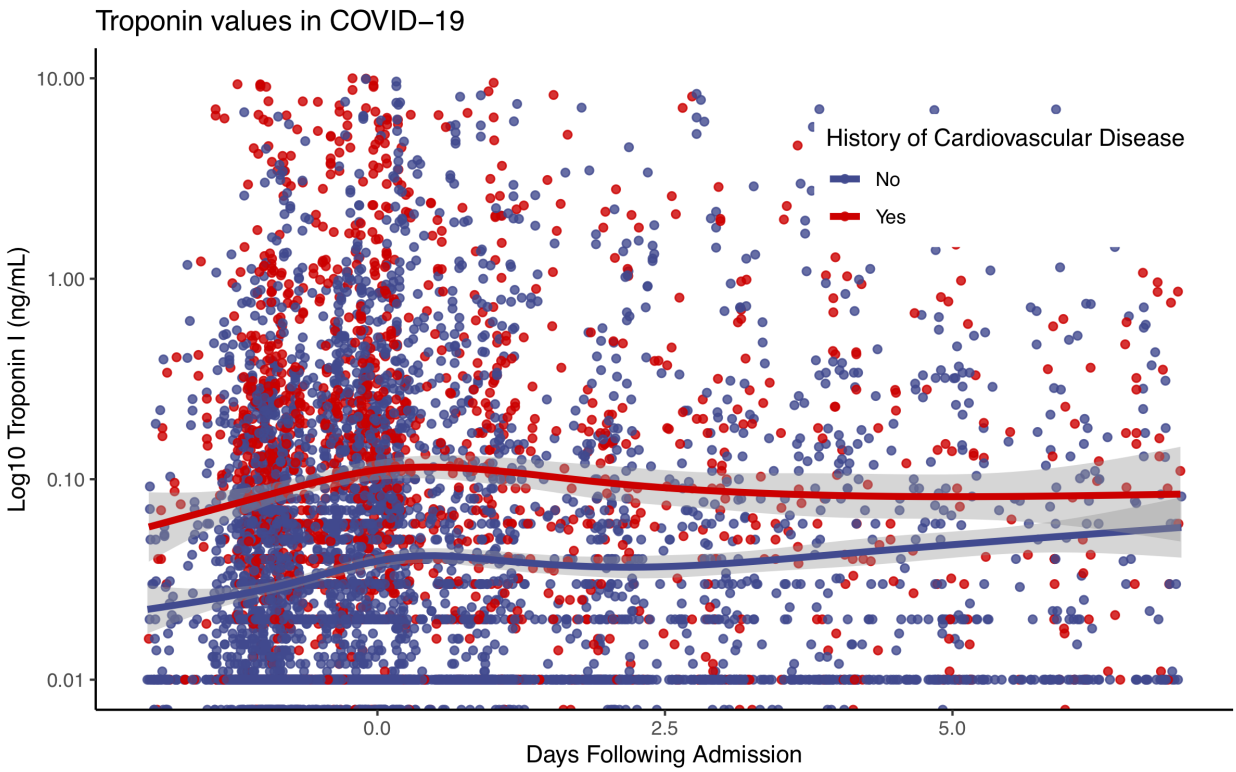
	[0.79, 2.75]	[0.73, 2.68]	[0.85, 2.82]	[0.91, 2.81]	
D-dimer above 1 mcg/mL (N (%))	1453 (66.2)	686 (61.9)	410 (69.6)	357 (71.8)	<0.001
	126.69	138.71	117.88	113.34	
C-reactive protein (median [IQR])	[63.71, 214.20]	[72.36, 223.43]	[61.33, 213.63]	[53.74, 193.88]	<0.001
	177.50	218.00	163.00	131.50	
Creatine kinase (median [IQR])	[83.25, 502.50]	[93.00, 487.25]	[70.75, 549.0]	[79.00, 425.75]	0.422
	441.00	456.00	436.00	409.50	
Lactate dehydrogenase (median [IQR])	[332.0, 592.0]	[351.25, 611.75]	[329.00, 574.0]	[305.00, 553.50]	<0.001
	780.50	814.00	743.00	765.00	
Ferritin (median (IQR))	[376, 1899]	[417.0, 1903.0]	[356.0, 1850.0]	[326.50, 1906.0]	0.12
	0.21	0.20	0.20	0.29	
Procalcitonin (median [IQR])	[0.09, 0.69]	[0.09, 0.57]	[0.09, 0.72]	[0.10, 0.95]	<0.001
	0.98	0.87	1.06	1.30	
Creatinine (median [IQR])	[0.75, 1.58]	[0.70, 1.20]	[0.78, 1.88]	[0.90, 2.54]	<0.001
	14.30	14.10	14.10	15.10 [	
Prothrombin time (pt) (median [IQR])	[13.50, 15.60]	[13.50, 15.10]	[13.30, 15.17]	13.90, 17.17]	<0.001

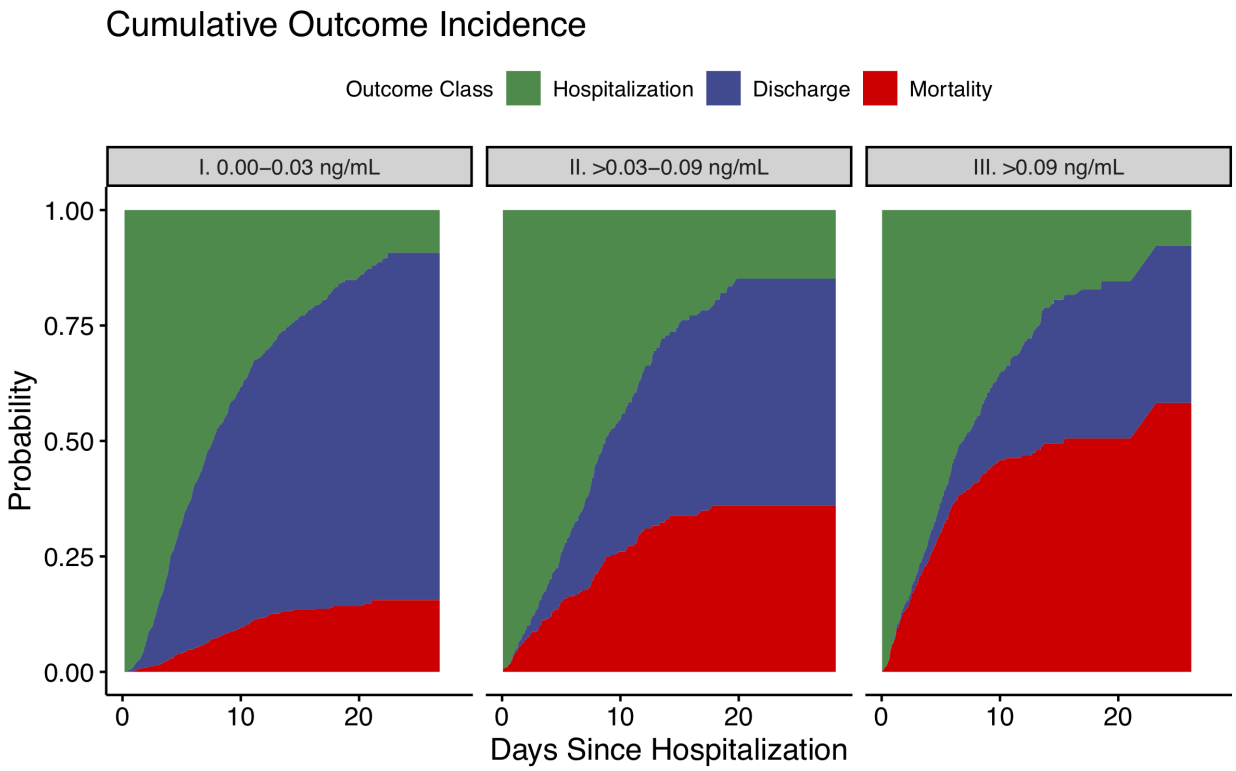
Partial thromboplastin time (aPTT)	32.90	32.30	32.00	35.70 [	
(median [IQR])	[29.52, 37.90]	[29.30, 36.20]	[29.25, 36.55]	31.20, 42.27]	0.002
	3.00	3.00	3.00	3.00	
Albumin (median [IQR])	[2.60, 3.30]	[2.60, 3.30]	[2.60, 3.30]	[2.60, 3.30]	0.703
	0.60	0.60	0.50	0.60	
Bilirubin (Total) (median [IQR])	[0.40, 0.80]	[0.40, 0.80]	[0.40, 0.70]	[0.40, 0.90]	0.002
	138.00	138.00	138.00	138.00	
Sodium (median [IQR])	[135.0, 141.0]	[135.0, 140.0]	[135.0, 141.0]	[135.0, 141.0]	0.057
Tachycardia (HR > 100 BPM) (N (%))	647 (23.6)	357 (26.0)	166 (23.5)	124 (18.9)	0.002
Fever (>38.0°C) (N (%))	517 (18.9)	283 (20.6)	143 (20.3)	91 (13.9)	0.001
Hypotension (SBP < 100 mmHg) (N (%))	228 (8.3)	111 (8.1)	58 (8.2)	59 (9.0)	0.762
SBP above 160 mmHg (N (%))	227 (8.3)	84 (6.1)	68 (9.6)	75 (11.5)	<0.001

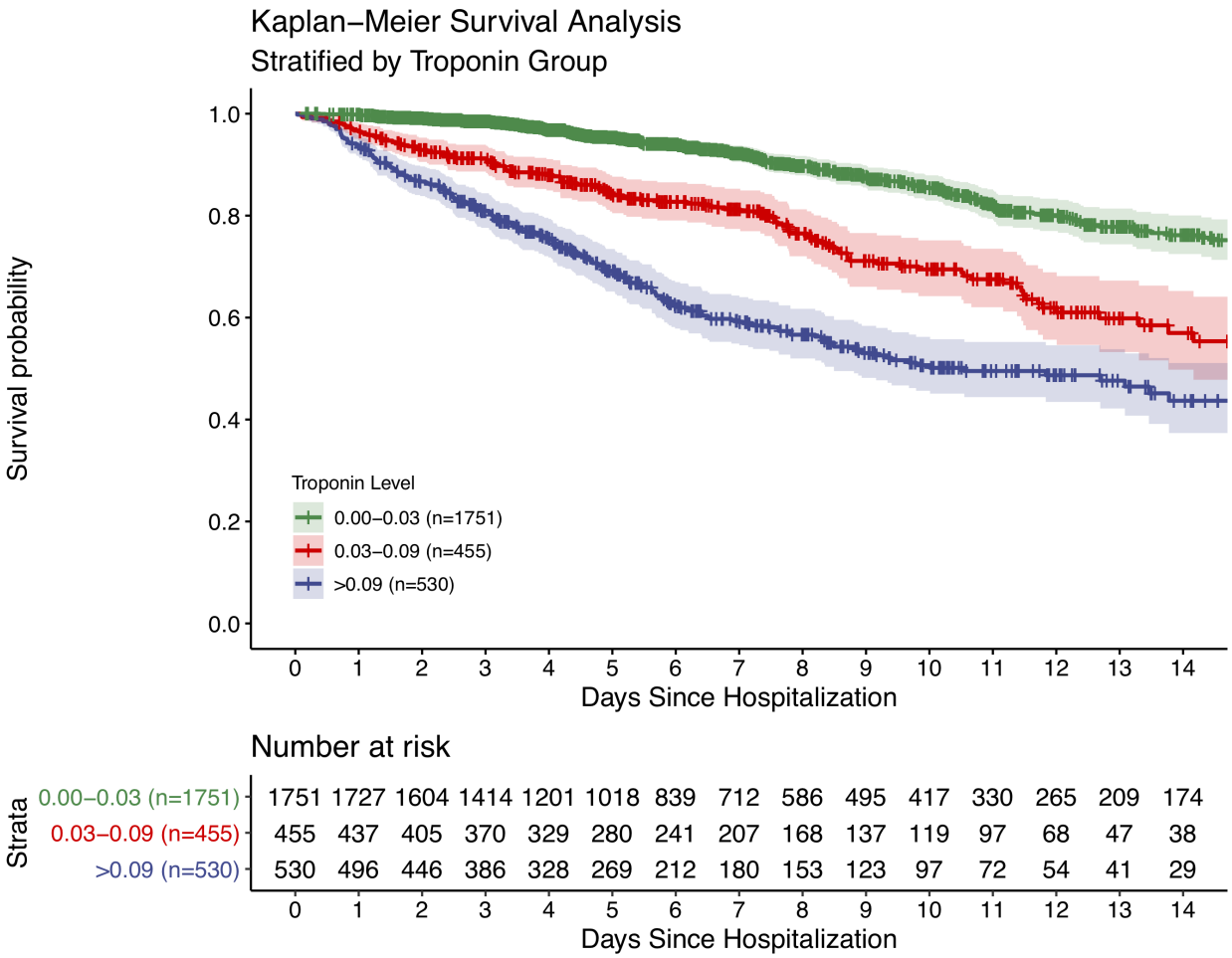
Table 3. Results from Cox proportional hazards regression analysis for mortality as a function of troponin strata, demographics, race, ethnicity, comorbidities, and clinical variables including BMI, CURB-65 score, ACEi/ARB use, and statin use.

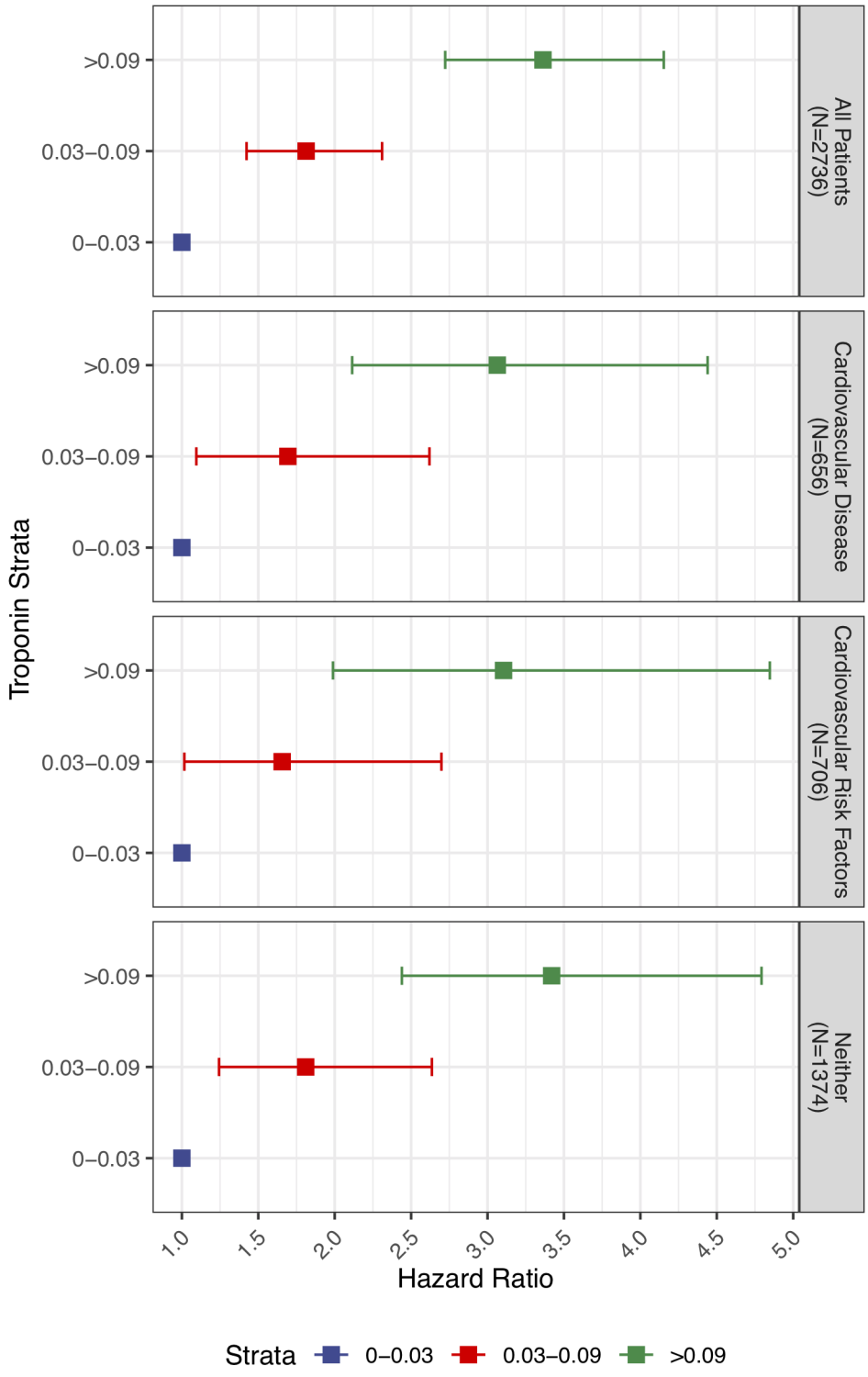
Multivariable Cox Regression Model for Mortality			
Coefficient	**OR**	**95% Confidence Interval**	**P Value**
Troponin Strata			
0.03-0.09 ng/mL	1.75	(1.37, 2.24)	<0.001
>0.09 ng/mL	3.03	(2.42, 3.80)	<0.001
Demographics			
Gender (Female)	0.85	(0.71, 1.03)	0.093
Age (Years)	1.04	(1.03, 1.04)	<0.001
Race			
African American	0.89	(0.70, 1.14)	0.371
Asian	0.95	(0.56, 1.61)	0.862
Pacific Islander	1.21	(0.49, 3.00)	0.681
Other	1.11	(0.85, 1.44)	0.451
Unknown	1.24	(0.77, 2.00)	0.378
Ethnicity			
Non-Hispanic/Latino	1.11	(0.84, 1.46)	0.479
Unknown	1.39	(1.01, 1.92)	0.045
Comorbidities			
Coronary Artery Disease	1.08	(0.85, 1.37)	0.535
Diabetes	1.01	(0.80, 1.27)	0.947
Heart Failure	1.03	(0.77, 1.37)	0.867
Hypertension	0.99	(0.79, 1.23)	0.905
Atrial Fibrillation	1.08	(0.81, 1.44)	0.586
Chronic Kidney Disease	1.02	(0.76, 1.36)	0.911
Clinical Variables			
Body Mass Index	1.02	(1.01, 1.03)	0.007
CURB-65 Score	1.23	(1.11, 1.36)	<0.001
ACE-I or ARB Use	1.05	(0.85, 1.31)	0.637
Statin Use	0.57	(0.47, 0.69)	<0.001








Kaplan–Meier Survival Analysis
Stratified by Troponin Group
Survival probability
1.0
0.8
0.6
0.4
0.2
0.0
Troponin Level
0.00–0.03 (n=1751)
0.03–0.09 (n=455)
>0.09 (n=530)
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Days Since Hospitalization
Number at risk
Strata
0.00–0.03 (n=1751) 1751 1727 1604 1414 1201 1018 839 712 586 495 417 330 265 209 174
0.03–0.09 (n=455) 455 437 405 370 329 280 241 207 168 137 119 97 68 47 38
>0.09 (n=530) 530 496 446 386 328 269 212 180 153 123 97 72 54 41 29
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Days Since Hospitalization


All Patients (N=2736)
Cardiovascular Disease (N=656)
Cardiovascular Risk Factors (N=706)
Neither (N=1374)
Troponin Strata
>0.09
0.03–0.09
0–0.03
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
Hazard Ratio
Strata
0–0.03
0.03–0.09
>0.09