Independent Predictors of Mortality in COVID-19 Myocardial Injury: The Role of Troponin Levels, GRACE Score, SOFA Score, and TIMI Score

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Abstract

Background
Coronavirus disease 2019 (COVID-19) infection is associated with troponin elevation, which is associated with increased mortality. However, it is not clear if troponin elevation is independently linked to increased mortality in COVID-19 patients. Although there is considerable literature on risk factors for mortality in COVID-19-associated myocardial injury, the Global Registry of Acute Coronary Events (GRACE), Thrombolysis in Myocardial Infarction (TIMI), and Sequential Organ Failure Assessment (SOFA) scores have not been studied in COVID-19-related myocardial injury. This data is important in risk-stratifying COVID-19 myocardial injury patients.

Methodology
Of the 1,500 COVID-19 patients admitted to our hospitals, 217 patients who had troponin levels measured were included. Key variables were collected manually, and univariate and multivariate cox regression analysis was done to determine the predictors of mortality in COVID-19-associated myocardial injury. The differences in clinical profiles and outcomes of COVID-19 patients with and without troponin elevation were compared.

Results
Mortality was 26.5% in the normal troponin group and 54.6% in the elevated troponin group. Patients with elevated troponins had increased frequency of hypotension (p = 0.01), oxygen support (p = 0.01), low absolute lymphocyte (p = 0.01), elevated blood urea nitrogen (p < 0.01), higher C-reactive protein (p < 0.01), higher D-dimer (p < 0.01), higher lactic acid (p < 0.01), and higher Quick SOFA (qSOFA), SOFA, TIMI, and GRACE (all scores p < 0.01). On univariate cox regression, troponin elevation (hazard ratio (HR) = 1.85, 95% confidence interval (CI) = 1.18-2.88, p = 0.01), TIMI score >3 (HR = 1.79, 95% CI = 1.11-2.75, p = 0.01), and GRACE score >140 (HR = 2.27, 95% CI = 1.46-3.55, p < 0.01) were highly associated with mortality, whereas troponin (HR = 1.18, 95% CI = 0.73-1.81, p = 0.52) were not. After adjusting for age, use of a non-rebreather or high-flow nasal cannula, hemoglobin <8.5 g/dL, suspected or confirmed source of infection, and qSOFA and SOFA scores (HR = 1.18, 95% CI = 1.07-1.29, p = 0.01) were independently associated with mortality, whereas troponin (HR = 1.08, 95% CI = 0.63-1.85, p = 0.76), TIMI score (HR = 1.02, 95% CI = 0.99-1.06, p = 0.12) and GRACE scores (HR = 1.01, 95% CI = 0.99-1.02, p = 0.10) were not associated with mortality.

Conclusions
Our study shows that troponin, GRACE score, and TIMI score are not independent predictors of mortality in COVID-19 myocardial injury. This may be because troponin elevation in COVID-19 patients may be related to demand ischemia rather than acute coronary syndrome-related. This was shown by the association of troponin with a higher degree of systemic inflammation and end-organ dysfunction. Therefore, we recommend SOFA scores in risk-stratifying COVID-19 patients with myocardial injury.

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Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic caused by a novel strain of coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Several studies have shown that myocardial injury is commonly seen in COVID-19 and is associated with a worse prognosis [1]. Although the exact mechanism is still under research, different mechanisms, such as supply-demand mismatch, microvascular thrombi formation, direct viral damage to myocytes, plaque destabilization due to inflammation, and cytokine storm, have been proposed [2,3]. Several retrospective cohort studies have been published on the prevalence and risk factors of troponin elevation in COVID-19 patients. The prevalence of troponin elevation ranges from 7% to 62%, depending upon the severity of COVID-19 [1,4-6]. Studies have shown that the degree of troponin elevation and the presence of cardiovascular disease and cardiovascular risk factors correlate with mortality in COVID-19 patients. The mortality rates among those with elevated troponin range from 20% to 61% [7-9].

However, studies have reported conflicting data on whether troponin is independently associated with mortality [7-9]. The Global Registry of Acute Coronary Events (GRACE) risk score and Thrombolysis in Myocardial Infarction (TIMI) scores predict mortality in patients with myocardial infarction, and the Sequential Organ Failure Assessment (SOFA) score predicts mortality in sepsis. However, the utility of these scores has not been studied in COVID-19-related myocardial injury. Therefore, our primary aim is to determine the independent predictors of mortality in COVID-19-related myocardial injury by comparing the differences in clinical profiles, laboratory values, and special scores of COVID-19 patients with and without troponin elevation. Our secondary aim is to study the predictive value of troponin, GRACE scores, TIMI scores, and SOFA scores on mortality through survival analysis.

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Materials And Methods

The electronic medical records of adult patients who were symptomatic for COVID-19 and tested positive for COVID-19 (SARS-CoV-2 reverse transcription polymerase chain reaction positive) from two centers from March 1, 2020, to December 31, 2020, were reviewed. A high-sensitivity troponin-I assay was used to divide patients into two categories. Patients who had troponin levels more than the upper limit of normal (troponin >ULN) were compared with patients who had troponin levels less than the upper limit of normal (troponin <ULN). The upper limit of normal corresponds to the 99th percentile of normal values for troponin. Demographics, clinical features, comorbidities, confounding factors for elevated troponin, vital signs, physical examination findings, laboratory values, troponin trends, electrocardiogram (EKG) changes, COVID-19 treatment, and special scores were collected on the day of troponin elevation. Some laboratory variables such as D-dimer, C-reactive protein (CRP), ferritin, and lactate dehydrogenase (LDH) were collected within seven days of the troponin test as they were not available on the day of troponin elevation. Data were extracted manually by trained investigators through standardized data collection manual. The institutional review board (IRB) of the appropriate institutions approved the study. The IRB waived informed consent due to the retrospective nature of the study.

Statistical analysis

Continuous data were reported as the median and interquartile range, and categorical data were reported as counts and percentages. Wilcoxon rank-sum test was used to analyze continuous data. The chi-square test was used to analyze categorical data. Survival analysis was done with the length of stay as the time variable and death or discharge from the hospital as right censoring. Survival graphs were reported as Kaplan-Meier survivor function with the log-rank test. We compared the clinical profiles, laboratory values, and special scores among patients who had troponin levels more than the upper limit of normal (troponin >ULN) with patients who had troponin levels less than the upper limit of normal (troponin <ULN). We initially ran a univariate cox regression to determine the predictors of mortality with elevated troponin. Variables that were significant in univariate analysis were incorporated in multivariate cox regression. We ran four separate models for troponin, TIMI score, GRACE score, and SOFA score to determine if these variables independently predicted mortality. Kaplan-Meier survival graphs were plotted for key variables with the log-rank test. Any variable with missing data of 10% or less was not included in the analysis. A p-value of less than or equal to 0.05 was considered significant. All data were analyzed with Stata Statistical Software: Release 17 (StataCorp LLC, College Station, TX, USA).

Results

Clinical features and comorbidities

After screening 1,500 COVID-19 patients, 217 patients who had troponin levels measured during any time of the hospital stay were included. Out of the 217 patients, 85 had elevated troponin, and 132 had normal troponin. Most patients had troponin levels measured during the first week of COVID-19 illness (median = 4, IQR = 1-8). The mean age was 63 (IQR = 50-77) years in the normal troponin group and 79 (IQR = 63-85) years in the elevated troponin group, and the difference was statistically significant (p < 0.01).
Cardiovascular diseases (p < 0.01) were associated with elevated troponin but not cardiovascular risk factors (p = 0.887). Patients with elevated troponins also had an increased likelihood of having a mean arterial pressure <65 mmHg (p = 0.01), increased respiratory rate (p = 0.04), increased oxygen support (p < 0.01), and rales on physical examination (p < 0.01) (Appendices).

**Laboratory values**

Patients with elevated troponin levels had lower absolute lymphocytes (p < 0.01), lower albumin (p < 0.01), higher blood urea nitrogen (p < 0.01), higher creatinine (p < 0.01), higher aspartate aminotransferase (p < 0.01), higher total bilirubin (p < 0.01), higher CRP (p < 0.01), lower LDH (p = 0.01), higher D-dimer (p < 0.01), and higher lactic acid (p < 0.01). Serial troponins were not available for 20% of patients. However, a delta change of 30% (positive or negative change) was more prevalent in patients with elevated troponin (p < 0.01). EKG changes such as tachyarrhythmia (p < 0.01), ST elevation (p < 0.01), ST depression (p < 0.01), and left ventricular hypertrophy (p = 0.02) were more prevalent in patients with elevated troponins (Appendices).

**Hospital course and outcomes**

In-hospital complications such as atrial fibrillation with rapid ventricular response rates (p < 0.01), congestive heart failure (p < 0.01), chronic obstructive pulmonary disease exacerbation (p < 0.01), intensive care unit (ICU) admission (p < 0.01), suspected or confirmed source of a bacterial infection (p < 0.01), intubation (p < 0.01), vasopressor use (p < 0.01), and death (p < 0.01) were more common in patients with elevated troponin. Higher Systemic Inflammatory Response System (SIRS), Quick SOFA (qSOFA), SOFA, TIMI, and GRACE scores were highly associated with elevated troponin levels (p < 0.01) (Appendices).

**Survival analysis**

Mortality was 26.5% in the normal troponin group and 54.6% in the elevated troponin group. Patients were categorized into three groups: troponin <ULN, troponin 1-3 times ULN, and troponin >3 ULN. The mortality in each group was 23.6%, 55.2%, and 59.6%, respectively. In unadjusted Cox regression, age (HR = 1.02, 95% CI = 1.00-1.04, p < 0.01), cardiomyopathy (HR = 2.25, 95% CI = 1.10-4.53, p = 0.02), and chronic kidney disease (HR = 1.38, 95% CI = 1.15-1.65) were statistically significant for mortality. Vitals signs such as heart rate >100 (HR = 1.82, 95% CI = 1.14-2.89), respiratory rate (HR = 1.03, 95% CI = 1.00-1.05), and the use of a non-rebreather or high-flow nasal cannula (HR = 1.72, 95% CI = 1.10-2.69) were associated with mortality. Among the laboratory values, hemoglobin <8.5 g/dL (HR = 3.04, 95% CI = 1.38-6.68, p < 0.01), anion gap >12 (HR = 1.66, 95% CI = 1.06-2.6, p = 0.02), serum albumin <3.1 g/dL (HR = 1.82, 95% CI = 1.17-2.84, p < 0.01), blood urea nitrogen (BUN) (HR = 1.00, 95% CI = 1.00-1.01, p = 0.04), tachyarrhythmia (HR = 2.32, 95% CI = 1.48-3.63, p < 0.01), and troponin elevation more than the upper limit of normal (HR = 1.85, 95% CI = 1.18-2.88, p < 0.01) were associated with mortality (Table 1).

| Variable                                      | Hazard ratio (95% confidence interval) | P-value |
|-----------------------------------------------|---------------------------------------|---------|
| Age                                           | 1.02 (1.00-1.04)                       | 0.033   |
| Race                                          |                                       |         |
| White                                         | Reference                              |         |
| Black                                         | 1.13 (0.60-2.02)                       | 0.67    |
| Hispanic                                      | 0.43 (0.20-0.98)                       | 0.030   |
| Asian                                         | 1.34 (0.82-2.16)                       | 0.542   |
| Comorbidities                                 |                                       |         |
| Myocardial infarction                         | 1.58 (0.88-2.88)                       | 0.121   |
| Cardiomyopathy                                | 2.23 (1.10-4.53)                       | 0.036   |
| Diabetes mellitus                             | 1.15 (0.73-1.81)                       | 0.529   |
| Hypertension                                  | 1.28 (0.76-2.15)                       | 0.344   |
| Statin use                                    | 0.05 (0.01-1.47)                       | 0.825   |
| Chronic kidney disease                        | 1.38 (1.15-1.65)                       | 0.000   |
| Hemodialysis or continuous renal replacement therapy | 167 (0.85-3.20)                  | 0.132   |
| Vitals                                        |                                       |         |
| Mean arterial pressure <65 mmHg               | 1.06 (0.85-1.35)                       | 0.118   |
| Parameter                                      | OR (95% CI)   | P-value |
|-----------------------------------------------|---------------|---------|
| Heart rate >100/minute                        | 1.02 (1.14-2.88) | 0.011   |
| Respiratory rate                              | 1.03 (1.00-1.06) | 0.017   |
| Noninvasive or high-flow nasal cannula        | 1.72 (1.10-2.86) | 0.016   |
| Labs                                          |               |         |
| Hemoglobin <8.5 g/dL                          | 3.04 (1.36-6.68) | 0.005   |
| Absolute lymphocytes <1 × 10^7/L              | 1.14 (0.75-1.78) | 0.582   |
| Serum sodium >145 mmol/L                      | 1.44 (0.62-3.34) | 0.382   |
| Anion gap >12                                 | 1.06 (1.06-2.6)  | 0.034   |
| Serum albumin <3.1 g/dL                       | 1.02 (1.17-2.84) | 0.007   |
| Blood urea nitrogen                           | 1.00 (1.00-1.01) | 0.04    |
| Creatinine >1 mg/dL                           | 1.42 (0.81-2.47) | 0.116   |
| Acute kidney injury                           | 1.51 (0.32-7.47) | 0.1     |
| Total bilirubin >1.2 mg/dL                    | 1.40 (0.71-2.54) | 0.288   |
| Estimated glomerular filtration rate >60 mm/hour | 1.21 (0.62-2.36) | 0.233   |
| D-dimer                                      | 1.00 (0.99-1.00) | 0.288   |
| C-reactive protein >100 mg/dL                 | 1.31 (0.83-2.08) | 0.239   |
| Electrocardiogram changes                     |               |         |
| Tachyarrhythmia                               | 2.32 (1.49-3.63) | 0.003   |
| ST elevation                                  | 1.68 (0.91-3.10) | 0.088   |
| ST depression                                 | 0.61 (0.15-2.52) | 0.503   |
| Left ventricular hypertrophy                  | 1.10 (0.44-2.75) | 0.855   |
| Troponin >ULN (upper limit of normal)         | 1.05 (1.19-2.88) | 0.007   |
| Delta change                                  | 1.07 (0.67-1.66) | 0.796   |
| Medications                                   |               |         |
| Antibiotics                                   | 1.69 (0.81-3.52) | 0.182   |
| Steroids                                      | 0.54 (0.34-0.85) | 0.008   |
| Remdesivir                                    | 0.61 (0.33-1.14) | 0.123   |
| Tocilizumab                                   | 0.62 (0.34-1.12) | 0.113   |
| Convalescent plasma                           | 0.53 (0.27-1.03) | 0.084   |
| Full-dose anticoagulation                     | 0.05 (0.04-1.32) | 0.483   |
| Prophylactic anticoagulation                  | 1.21 (0.77-1.95) | 0.494   |
| Antiplatelets                                 | 1.73 (1.10-2.72) | 0.016   |
| ICU                                           | 1.83 (1.11-2.91) | 0.016   |
| Intubation                                    | 1.45 (0.92-2.27) | 0.196   |
| Vasopressor                                   | 1.53 (0.86-2.46) | 0.073   |
| Scores                                        |               |         |
| Suspected or confirmed infection              | 2.7 (1.71-4.23) | 0.000   |
| SIRS features                                 | 1.27 (1.04-1.55) | 0.017   |
| SOFA >1                                       | 2.12 (1.29-3.51) | 0.003   |
| SOFA >4                                       | 2.29 (1.46-3.57) | 0.000   |
The use of antiplatelet (HR = 1.73, 95% CI = 1.10-2.72, p = 0.01) and corticosteroids (HR = 0.54, 95% CI = 0.34-0.85, p < 0.01) were associated with lower mortality. The presence of a confirmed or suspected bacterial infection (HR = 2.7, 95% CI = 1.71-4.25, p < 0.01) and ICU stay (HR = 1.80, 95% CI = 1.11-2.91, p = 0.01) were associated with increased mortality. The presence of systemic inflammatory response syndrome features (HR = 1.27, 95% CI = 1.04-1.55, p = 0.01), qSOFA score >1 (HR = 2.12, 95% CI = 1.29-3.51, p < 0.01), SOFA >4 (HR = 2.29, 95% CI = 1.46-3.57, p < 0.01), TIMI score >3 (HR = 1.79, 95% CI = 1.11-2.75, p = 0.01), GRACE >140 (HR = 2.27, 95% CI = 1.45-3.55, p < 0.01) were all highly associated with mortality. The Kaplan-Meier survival curves plotted for troponin, GRACE, TIMI, and SOFA scores were significant based on the log-rank test (Figure 1).

When combined, cardiovascular disease (HR = 1.40, 95% CI = 0.89-2.21, p = 0.129) and cardiovascular risk factors (HR = 1.15, 95% CI = 0.73-1.81, p = 0.52) were not associated with mortality. We created four separate multivariate Cox regression models for troponin, GRACE score, and TIMI score while adjusting for age, non-rebreather or high-flow nasal cannula, hemoglobin <8.5 g/dL, suspected or confirmed source of infection, and SOFA score. Troponin elevation (HR = 0.79, 95% CI = 0.46-1.34, p = 0.392), TIMI score (HR = 1.03, 95% CI = 0.99-1.07, p = 0.078), and GRACE score (HR = 1.01, 95% CI = 0.99-1.02, p = 0.108) were not independently associated with mortality. SOFA score (HR = 1.18, 95% CI = 1.07-1.29) was strongly associated with mortality in all models (Tables 2-4).

### TABLE 1: Univariate Cox regression for key variables.

| Variable          | Hazard Ratio | 95% CI       | p-value |
|-------------------|--------------|--------------|---------|
| Timi score >3     | 1.79         | (1.11-2.75)  | 0.016   |
| GrACE >140        | 2.27         | (1.45-3.55)  | 0.000   |

ICU: intensive care unit; SOFA: Sequential Organ Failure Assessment; qSOFA: Quick SOFA; TIMI: Thrombolysis in Myocardial Infarction; GRACE: Global Registry of Acute Coronary Events

FIGURE 1: Kaplan-Meier survival analysis for TIMI score >3 (A), GRACE score >140 (B), Troponin >ULN (C), and SOFA score >4 (D).

The p-value in the figures represents the p-value in the log-rank test.

The x-axis represents the cumulative patients at risk expressed as a fraction, and the y-axis represents the length of stay in days.

ULN: upper limit of normal; SOFA: Sequential Organ Failure Assessment; TIMI: Thrombolysis in Myocardial Infarction; GRACE: Global Registry of Acute Coronary Events
### TABLE 2: Multivariate Cox regression model for troponin.

SOFA: Sequential Organ Failure Assessment

| Variable                                | Hazard ratio (95% confidence interval) | P-value |
|-----------------------------------------|---------------------------------------|---------|
| Age                                     | 1.04 (1.01-1.06)                      | 0.000   |
| High-flow or non-rebreather use          | 1.80 (1.07-3.03)                      | 0.025   |
| Hemoglobin <8.5 g/dL                    | 5.17 (1.89-14.12)                     | 0.001   |
| Suspected or confirmed source of bacterial infection | 2.72 (1.64-4.46) | 0.000   |
| SOFA score                              | 1.18 (1.07-1.29)                      | 0.000   |
| Troponin                                | 0.79 (0.46-1.34)                      | 0.380   |

### TABLE 3: Multivariate cox regression model for TIMI score.

SOFA: Sequential Organ Failure Assessment; TIMI: Thrombolysis in Myocardial Infarction

| Variable                                | Hazard ratio (95% confidence interval) | P-value |
|-----------------------------------------|---------------------------------------|---------|
| Age                                     | 1.03 (1.01-1.05)                      | 0.001   |
| High-flow or non-rebreather use          | 1.83 (1.08-3.11)                      | 0.024   |
| Hemoglobin <8.5 g/dL                    | 4.90 (1.80-13.6)                      | 0.002   |
| Suspected or confirmed source of bacterial infection | 2.81 (1.72-4.61) | 0.000   |
| SOFA score                              | 1.17 (1.07-1.27)                      | 0.000   |
| TIMI score                              | 1.03 (0.99-1.07)                      | 0.078   |

### TABLE 4: Multivariate cox regression model for GRACE score.

SOFA: Sequential Organ Failure Assessment; GRACE: Global Registry of Acute Coronary Events

| Variable                                | Hazard ratio (95% confidence interval) | P-value |
|-----------------------------------------|---------------------------------------|---------|
| Age                                     | 1.01 (0.97-1.05)                      | 0.001   |
| High-flow or non-rebreather use          | 1.81 (1.07-3.07)                      | 0.024   |
| Hemoglobin <8.5 g/dL                    | 4.79 (1.72-13.3)                      | 0.002   |
| Suspected or confirmed source of bacterial infection | 2.62 (1.41-4.85) | 0.000   |
| SOFA score                              | 1.11 (1.01-1.23)                      | 0.000   |
| GRACE score                             | 1.01 (0.99-1.02)                      | 0.108   |

### Discussion

Similar to prior literature, patients with troponin elevation were older and more likely to have cardiovascular diseases such as coronary artery disease, heart failure, cardiomyopathy, stroke, and atrial fibrillation. Patients with elevated troponin also had a higher prevalence of cardiovascular risk factors such as hypertension, diabetes, dyslipidemia, smoking history, chronic kidney disease, and hemodialysis or continuous renal replacement therapy [1,4-6,10]. In addition, the association of hypotension, tachypnea, increased oxygen requirement, lymphopenia, anion gap acidosis, lower albumin, higher BUN and creatinine,
and higher inflammatory markers (D-dimer, CRP, LDH) indicates the presence of a higher degree of sepsis and organ dysfunction in patients with elevated troponin when compared with patients with normal troponin. Moreover, the SIRS, qSOFA, and SOFA scores were highly associated with elevated troponin.

There is conflict in current data on whether cardiovascular diseases and cardiovascular risk factors are independently associated with mortality [7–9]. In our cohort, cardiovascular diseases and cardiovascular risk factors were not associated with mortality. In addition, studies are conflicting on whether troponin elevation is independently associated with mortality. One study showed that troponin elevation is independently associated with mortality only in patients with echocardiographic abnormalities [7]. Given that troponin elevation is not independently associated with mortality, it is unclear if obtaining routine troponin levels would change the management of COVID-19 patients. Our study shows that age, hemoglobin <8.5 g/dL, high oxygenation requirements, SOFA scores, and suspected or confirmed source of bacterial infection independently predicted mortality in COVID-19-related myocardial injury. Hence, these variables can be used for risk stratification of COVID-19 patients with elevated troponin.

It is important to distinguish type 1 from type 2 myocardial injury in COVID-19 patients as management is different [11]. Type 1 myocardial injury is due to acute plaque rupture causing coronary artery thrombosis. Type 2 myocardial injury is due to a supply-demand mismatch with or without pre-existing atherosclerosis. For COVID-19 patients suspected of type 1 myocardial injury, an early invasive strategy with dual antiplatelet therapy, statin, beta-blocker, and anticoagulation may be warranted. However, when a COVID-19 patient is suspected of having type 2 myocardial injury, treatment involves supportive care and management of sepsis. Although there is no definitive way to distinguish between the two subtypes other than cardiac catheterization, echocardiographic assessment to study wall motion abnormalities may be useful, as shown in this study [7]. As it is not possible to subject all COVID-19 patients with myocardial injury to cardiac catheterization, we hypothesize that in addition to clinical presentation and echocardiography, the SOFA score may be used to differentiate type 1 from type 2 myocardial injury.

The SOFA score is the gold standard for predicting sepsis mortality [12]. The SOFA score involves seven variables to assess organ function. These include PaO2/FiO2 ratio, mechanical ventilation, thrombocytopenia, Glasgow Coma Scale score, mean arterial pressure, use of vasopressors, and creatinine and bilirubin levels [12]. This encompasses respiratory, hematological, neurological, cardiovascular, renal, and hepatic markers of sepsis. TIMI and GRACE scores are considered the gold standard to predict mortality in type 1 myocardial injury [13,14]. The TIMI score involves age, the number of cardiovascular risk factors, known coronary artery disease, recent aspirin use, recent severe angina, EKG changes, and troponin elevation. In addition to age, ST deviation on EKG, and elevated troponin, the GRACE score also involves heart rate, systolic blood pressure, creatinine, cardiac arrest, and Killip class [14].

In our study, SOFA scores were independently associated with mortality in COVID-19-related myocardial injury, whereas GRACE and TIMI scores were not independently associated with mortality. This is likely due to the possibility of most patients having type 2 myocardial injury in COVID-19. Although we did not perform cardiac catheterization, it can be safely inferred that troponin elevation in COVID-19 was mainly due to demand ischemia from sepsis rather than acute coronary thrombosis in our cohort. In such patients, management should focus on treating COVID-19 sepsis, not myocardial injury. Patients with low SOFA scores and a higher degree of troponin elevation may have a true type 1 myocardial injury, and these patients may need early catheterization and management for acute coronary syndrome. However, we need more studies comparing type 1 and 2 myocardial injury to make this inference. Limitations of our study include a dual-center design, a small sample size, and the lack of cardiac catheterization data. Our study is one of the few studies which has evaluated the role of GRACE, SOFA, and TIMI scores in COVID-19-associated myocardial injury.

Conclusions

Our study shows that the SOFA score independently predicts mortality, whereas troponin, GRACE, and TIMI scores do not independently predict mortality in COVID-19-associated myocardial injury. This association suggests the possibility of a preponderance of type 2 myocardial injury in COVID-19 instead of type 1 myocardial injury. Troponin is a cardiac enzyme, and it can be elevated in a variety of disorders, especially severe sepsis. Patients with elevated troponin had higher crude mortality rates. However, after adjusting for markers of sepsis, troponin elevation was not independently associated with elevated mortality. Therefore, we recommend the SOFA score in risk-stratifying COVID-19 patients. The role of the SOFA score in differentiating COVID-19-associated type 1 and 2 myocardial injury is an area of future research.

Appendices

History and physical examination of troponin elevation in COVID-19

Patients with elevated troponin had a lower BMI (p = 0.03). Fewer Hispanics had troponin elevation when compared with whites (32% of Hispanics with normal troponin and 7.9% with elevated troponin, p < 0.01). None of the clinical features of COVID-19, such as myalgia, fever, cough, sputum, dyspnea, chest pain, and pleuritic chest pain, were different between the two groups.
Patients with elevated troponin had an increased likelihood of having a history of myocardial infarction (p < 0.01), congestive heart failure (p < 0.01), atrial fibrillation (p < 0.01), cardiomyopathy (p < 0.01), diabetes mellitus (p = 0.02), hypertension (p < 0.01), dyslipidemia (p = 0.02), chronic kidney disease (p < 0.01), smoking (p < 0.01), recent surgery (p = 0.01), hematologic malignancy (p < 0.01), and continuous renal replacement therapy or hemodialysis (p < 0.01) when compared to patients who had normal troponin. In summary, cardiovascular diseases (p < 0.01) were associated with elevated troponin but not cardiovascular risk factors (p = 0.887).

Patients with elevated troponin also had an increased likelihood of having a mean arterial pressure <65 mmHg (p = 0.01), increased respiratory rate (p = 0.04), increased oxygen support (p < 0.01), and rales on physical examination (p < 0.01). Other vital signs were not different between both groups. Rare causes for elevated troponin were studied to exclude significant confounding. This includes current burns, physical exertion, recent ablation, pacemaker firing, cardioversion/implantable cardioverter-defibrillator shocks, open heart surgery, heart biopsy, closure of atrial septal defects, biotin use, infectious mononucleosis, and trauma. These variables were mostly absent in our cohort.

| Variable                   | Normal troponin | Elevated troponin (troponin >ULN) | P-value |
|----------------------------|-----------------|-----------------------------------|---------|
| N = 132                    | N = 85          |                                   |         |
| Age                        |                 |                                   |         |
|                            | 63 (50-77)      | 79 (63-85)                        | 0.000   |
| Male sex                   |                 |                                   |         |
|                            | 70 (53.4%)      | 45 (52.9%)                        | 0.035   |
| Body mass index            |                 |                                   |         |
|                            | 29.1 (20-33.5)  | 27 (23.5-32.2)                    | 0.033   |
| Race                       |                 |                                   |         |
| White                      |                 |                                   |         |
|                            | 42 (41.7%)      | 38 (60.3%)                        |         |
| Black                      |                 |                                   |         |
|                            | 19 (14.4%)      | 15 (25.3%)                        | 0.06    |
| Hispanic                   |                 |                                   |         |
|                            | 33 (25.2%)      | 5 (7.9%)                          | 0.007   |
| Asian                      |                 |                                   |         |
|                            | 5 (8.7%)        | 4 (6.3%)                          | 0.288   |
| Duration of COVID-19 illness |              |                                   |         |
|                            | 4 (1-6)         | 2 (1-7)                           | 0.417   |
| Clinical symptoms          |                 |                                   |         |
| Myalgia                    |                 |                                   |         |
|                            | 34 (26.1%)      | 26 (31.7%)                        | 0.453   |
| Fever                      |                 |                                   |         |
|                            | 86 (65%)        | 40 (67%)                          | 0.527   |
| Cough                      |                 |                                   |         |
|                            | 77 (58.3%)      | 40 (68.1%)                        | 0.159   |
| Sputum                     |                 |                                   |         |
|                            | 14 (10.6%)      | 11 (13.1%)                        | 0.627   |
| Dyspnea                    |                 |                                   |         |
|                            | 87 (64.4%)      | 57 (67%)                          | 0.052   |
| Chest pain                 |                 |                                   |         |
|                            | 29 (22.1%)      | 9 (10.7%)                         | 0.086   |
| Pleuritic chest pain       |                 |                                   |         |
|                            | 7 (5.3%)        | 1 (1.1%)                          | 0.111   |
| Comorbidities              |                 |                                   |         |
| Myocardial infarction      |                 |                                   |         |
|                            | 12 (9%)         | 20 (25.5%)                        | 0.001   |
| Congestive heart failure   |                 |                                   |         |
|                            | 14 (10.6%)      | 24 (27.9%)                        | 0.001   |
| Atrial fibrillation        |                 |                                   |         |
|                            | 13 (9.8%)       | 20 (24.7%)                        | 0.006   |
| Cardiomyopathy             |                 |                                   |         |
|                            | 4 (3%)          | 12 (13.9%)                        | 0.003   |
| Stroke                     |                 |                                   |         |
|                            | 10 (7.5%)       | 7 (8.1%)                          | 0.911   |
| Diabetes mellitus          |                 |                                   |         |
|                            | 50 (37.8%)      | 32 (37.6%)                        | 0.02    |
| Hypertension               |                 |                                   |         |
|                            | 74 (54%)        | 67 (77.9%)                        | 0.001   |
| Dyslipidemia               |                 |                                   |         |
|                            | 55 (41.6%)      | 48 (55.8%)                        | 0.029   |
| COPD                       |                 |                                   |         |
|                            | 13 (9.8%)       | 10 (11.6%)                        | 0.712   |
| Pulmonary hypertension     |                 |                                   |         |
|                            | 2 (1.5%)        | 2 (2.3%)                          | 0.689   |
| Condition                                      | Group 1   | Group 2   | p-value |
|------------------------------------------------|-----------|-----------|---------|
| Solid cancer                                   | 14 (10.4%)| 10 (11.4%)| 0.882   |
| Hematologic cancer                             | 0         | 6 (6.8%)  | 0.002   |
| Chemotherapy for cancer                        | 3 (2.2%)  | 3 (3.4%)  | 0.669   |
| Chronic kidney disease                         | 23 (17.4%)| 22 (25.8%)| 0.065   |
| History of organ transplant                    | 1 (0.7%)  | 0         | 0.414   |
| Liver disease                                  | 4 (3%)    | 1 (1.1%)  | 0.398   |
| Smoking                                        | 31 (23.4%)| 7 (8.1%)  | 0.069   |
| Alcohol abuse                                  | 13 (9.8%) | 9 (10.4%) | 0.619   |
| Recent surgery                                 | 4 (3%)    | 10 (11.7%)| 0.012   |
| Hemodialysis or continuous renal replacement   | 3 (2.2%)  | 9 (10.4%) | 0.011   |
| therapy                                        |           |           |         |
| Any cardiovascular disease                     | 33 (25%)  | 49 (56.9%)| 0.000   |
| Any cardiovascular risk factors                | 50 (37.8%)| 32 (37.2%)| 0.887   |
| Rare causes of elevated troponin               |           |           |         |
| Current burns                                  | 0         | 0         |         |
| Physical exertion                              | 0         | 2 (2.3%)  | 0.08    |
| Recent ablation                                | 1 (0.7%)  | 0         | 0.414   |
| Pacemaker                                      | 4 (3%)    | 5 (5.8%)  | 0.328   |
| Cardioversion/ICD shocks                       | 0         | 0         |         |
| Heart biopsy/open heart surgery/closure of ASD | 0         | 0         |         |
| Bioaerol                                     | 0         | 1 (1.1%)  | 0.219   |
| Infectious mononucleosis                       | 0         | 2 (2.2%)  | 0.081   |
| Trauma                                         | 1 (0.76%) | 1 (1.1%)  | 0.77    |
| Physical examination                           |           |           |         |
| Systolic blood pressure (mm/Hg)                | 128 (114-140) | 123 (111-150) | 0.789 |
| Diastolic blood pressure (mm/Hg)               | 73 (64-80)  | 70 (60-81)  | 0.522   |
| Mean arterial pressure -65 mm/Hg              | 2 (1.5%)   | 7 (6%)     | 0.018   |
| Maximum temperature (°F)                       | 98.9 (98.3-100) | 98.8 (98.1-102.2) | 0.684 |
| Heart rate (beats/minute)                      | 90 (80-103) | 92 (80-100) | 0.074   |
| Respiratory rate (per minute)                  | 20 (19-24) | 22 (19-28) | 0.04    |
| Oxygen saturation (%)                          | 96 (94-97) | 95 (90-98) | 0.615   |
| Oxygenation device                              |           |           |         |
| Room air                                       | 93 (71-14) | 45 (22.3%) | 0.006   |
| Nasal cannula                                  | 12 (9%)   | 20 (23.2%)|         |
| High-flow nasal cannula                        | 21 (15.9%)| 8 (9.3%)  |         |
| Jugular venous distension                      | 2 (1.5%)  | 0         | 0.246   |
| Rate                                           | 15 (11-4%)| 22 (25.8%)| 0.007   |

**TABLE 5: History and physical examination of COVID-19 myocardial injury patients.**

COVID-19: coronavirus disease 2019; ULN: upper limit of normal; COPD: chronic obstructive pulmonary disease; ICD: implantable cardioverter-defibrillator; ASD: atrial septal defect
| Variable                        | Normal troponin | Elevated troponin (troponin >ULN) | P-value |
|--------------------------------|----------------|-----------------------------------|---------|
| Laboratory values              |                |                                   |         |
| Total white count (10^9/L)     | 7.05 (5.26-9.35) | 7.8 (5.8-11.0)                   | 0.1     |
| Hemoglobin (g/dL)              | 12.8 (11.3-14.4) | 12.2 (10.8-13.8)                 | 0.127   |
| Platelets (10^9/L)             | 207 (151-273)   | 183 (145-241)                    | 0.11    |
| Bands                          | 0 (0-4)         | 0 (0-4)                           | 0.27    |
| Absolute neutrophil (10^9/L)   | 6.1 (3.8-11.6)  | 6.3 (4.3-10.7)                   | 0.942   |
| Absolute lymphocytes (10^9/L)  | 1.1 (0.7-3.4)   | 0.7 (0.3-1.2)                    | 0.900   |
| Serum sodium (mmol/L)          | 135 (133-138)   | 137 (133-141)                    | 0.005   |
| Serum potassium (mEq/L)        | 4 (3.7-4.3)     | 4.1 (3.8-4.6)                    | 0.03    |
| Serum calcium (mg/dL)          | 8.4 (7.1-10.1)  | 8.5 (7.8-10.0)                   | 0.795   |
| Blood glucose (mg/dL)          | 115 (102-125)   | 138 (127-174)                    | 0.087   |
| Anion gap                      | 9 (7-12)        | 11 (9-14)                        | 0.000   |
| Serum magnesium (mg/dL)        | 1.8 (1.5-2.1)   | 2.1 (1.7-2.2)                    | 0.059   |
| Serum chloride (mEq/L)         | 101 (97-104)    | 102 (100-108)                    | 0.088   |
| Albumin (g/dL)                 | 3.4 (3.1-3.8)   | 3.1 (2.8-3.6)                    | 0.000   |
| Blood urea nitrogen (mg/dL)    | 16.5 (11-27)    | 34.5 (12.5-54.6)                 | 0.000   |
| Serum creatinine (mg/dL)       | 0.96 (0.78-1.41) | 1.46 (1.2-2.6)                | 0.000   |
| Acute kidney injury            | 84 (64%)        | 48 (55%)                         | 0.185   |
| Alkaline phosphatases (U/L)    | 77 (62-91)      | 78 (111-161)                     | 0.547   |
| Aspartate aminotransferase (U/L)| 30 (23-54)  | 46 (32-64)                      | 0.002   |
| Alanine aminotransferase (U/L) | 29 (20-42)    | 28 (19-54)                      | 0.866   |
| Total bilirubin (mg/dL)        | 0.3 (0.4-0.7)   | 0.7 (0.5-0.9)                    | 0.002   |
| D-dimer (ng/mL)                | 610 (238-1,180) | 1,060 (273-3,946)               | 0.098   |
| CRP (mg/mL)                    | 79 (20-149)     | 139 (68-201)                     | 0.002   |
| LDH (U/L)                      | 532 (232-482)   | 285 (296-509)                    | 0.012   |
| Lactic acid (mmol/L)           | 1.5 (1.2-1.3)   | 1.9 (1.3-3)                      | 0.004   |
| Serial troponin (ng/mL)        |                |                                   |         |
| First troponin                 | 0.03 (0.02-0.03) | 0.33 (0.14-0.76)            | 0.000   |
| Second troponin                | 0.04 (0.03-0.07) | 0.40 (0.22-1.65)            | 0.000   |
| Third troponin                 | 0.06 (0.03-0.13) | 0.45 (0.21-1.9)            | 0.01    |
| EKG changes                    |                |                                   |         |
| Tachyarrhythmia                | 15 (11.4%)      | 36 (44.4%)                       | 0.000   |
| Bradyarrhythmia                | 2 (2%)          | 2 (2.4%)                         | 0.654   |
| ST elevation                   | 4 (3%)          | 6 (9.7%)                         | 0.008   |
| ST depression                  | 1 (0.76%)       | 6 (7.3%)                         | 0.01    |
| Left ventricular hypertrophy   | 5 (3.8%)        | 10 (12.2%)                       | 0.022   |
| Condition                                | COVID-19 | Control | p-value |
|------------------------------------------|----------|---------|----------|
| PR segment depression                    | 0        | 2 (4%)  | 0.075    |
| In-hospital complications                |          |         |          |
| Multifocal pneumonia                     | 84 (63.6%) | 58 (58.5%) | 0.433 |
| Atrial fibrillation with rapid ventricular rate | 9 (6.8%)  | 18 (19%) | 0.000 |
| Pulmonary embolism                       | 1 (0.7%)  | 1 (1.2%) | 0.75    |
| Congestive heart failure                 | 1 (0.7%)  | 18 (20.5%) | 0.000 |
| Acedile stroke                           | 0        | 1 (1.1%) | 0.213 |
| COPD exacerbation                        | 3 (1.3%)  | 1 (1.1%) | 0.825    |
| ICU admission                            | 32 (24.2%) | 42 (48.8%) | 0.000 |
| Intubation                               | 24 (18.1%) | 28 (32.7%) | 0.011 |
| Vasopressor                              | 12 (9%)   | 21 (23.3%) | 0.002    |
| Death                                    | 35 (26.5%) | 47 (54.6%) | 0.000 |
| Length of stay                           | 6 (3-12)  | 6 (4-12) | 0.223 |

### Treatment

| Treatment                      | COVID-19 | Control | p-value |
|--------------------------------|----------|---------|----------|
| Antibiotics                    | 86 (65.1%) | 64 (75.2%) | 0.171 |
| Plaquenil                      | 61 (46.2%) | 27 (31.7%) | 0.026 |
| Steroids                       | 57 (43.1%) | 42 (49.4%) | 0.441 |
| Remdesivir                     | 18 (13.6%) | 18 (21.1%) | 0.164 |
| Tocilizumab                    | 17 (12.8%) | 7 (8.2%) | 0.266 |
| Convalescent plasma            | 10 (8%) | 8 (10.2%) | 0.627 |
| Full-dose anticoagulation      | 33 (25%) | 43 (50%) | 0.627 |
| Prophylactic anticoagulation   | 65 (50%) | 42 (49.4%) | 0.030 |
| Antplatelet                    | 29 (21.9%) | 41 (47.6%) | 0.824 |
| Treated as MI                  | 4 (3%) | 17 (19.7%) | 0.000 |
| Stress test                    | 1 (0.7%) | 0 | 0.3 |
| Catheterization                | 0 | 0 |          |

### Sepsis scores

| Sepsis score | COVID-19 | Control | p-value |
|--------------|----------|---------|----------|
| SIRS         | 1 (1-2) | 2 (1-2) | 0.032 |
| qSOFA        | 1 (1-1) | 1 (0-2) | 0.000 |
| SOFA         | 2 (1-3) | 4 (2-5) | 0.000 |
| Suspected or confirmed source of infection | 20 (21.9%) | 38 (44.4%) | 0.000 |

### MI scores

| MI score | COVID-19 | Control | p-value |
|----------|----------|---------|----------|
| TIMI score | 1 (0-2) | 3 (2-4) | 0.030 |
| GRACE score | 90 (60-112) | 142 (114-158) | 0.000 |

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**TABLE 6: Laboratory values and outcomes in COVID-19-associated myocardial injury.**

COVID-19: coronavirus disease 2019; ULN: upper limit of normal; CRP: C-reactive protein; LDH: lactate dehydrogenase; EKG: electrocardiogram; COPD: chronic obstructive pulmonary disease; ICU: intensive care unit; MI: myocardial injury; SIRS: Systemic Inflammatory Response System; SOFA: Sequential Organ Failure Assessment; qSOFA: Quick SOFA; TIMI: Thrombolysis in Myocardial Infarction; GRACE: Global Registry of Acute Coronary Events
Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. Saint Peter’s University Hospital issued approval 20:50. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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