2020

Usefulness of Elevated Troponin to Predict Death in Patients with COVID-19 and Myocardial Injury.

D. T. Majure
Zucker School of Medicine at Hofstra/Northwell, dmajure@northwell.edu

L. Gruberg
Zucker School of Medicine at Hofstra/Northwell, lgruberg@northwell.edu

S. G. Saba
Zucker School of Medicine at Hofstra/Northwell, ssaba1@northwell.edu

C. Kvasnovsky

J. S. Hirsch
Zucker School of Medicine at Hofstra/Northwell, jhirsch8@northwell.edu

See next page for additional authors

Authors

D. T. Majure, L. Gruberg, S. G. Saba, C. Kvasnovsky, J. S. Hirsch, R. Jauhar, and Northwell Health COVID-19 Research Consortium

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

Usefulness of Elevated Troponin to Predict Death in Patients With COVID-19 and Myocardial Injury

David T. Majure, MD, MPH[a,b,*], Luis Gruberg, MD[c], Shahryar G. Saba, MD[a,b], Charlotte Kvasnovsky, MD, PhD, MPH[a], Jamie S. Hirsch, MD, MA, MSB[d,e,f], and Rajiv Jauhar, MD[a,b], for the Northwell Health COVID-19 Research Consortium

Elevations in troponin levels have been shown to predict mortality in patients with coronavirus disease 2019 (COVID-19). The role of inflammation in myocardial injury remains unclear. We sought to determine the association of elevated troponin with mortality in a large, ethnically diverse population of patients hospitalized with COVID-19, and to determine the association of elevated inflammatory markers with increased troponin levels. We reviewed all patients admitted at our health system with COVID-19 from March 1 to April 27, 2020, who had a troponin assessment within 48 hours of admission. We used logistic regression to calculate odds ratios (ORs) for mortality during hospitalization, controlling for demographics, co-morbidities, and markers of inflammation. Of 11,159 patients hospitalized with COVID-19, 6,247 had a troponin assessment within 48 hours. Of these, 4,426 (71%) patients had normal, 919 (15%) had mildly elevated, and 902 (14%) had severely elevated troponin. Acute phase and inflammatory markers were significantly elevated in patients with mildly and severely elevated troponin compared with normal troponin. Patients with elevated troponin had significantly increased odds of death for mildly elevated compared with normal troponin (adjusted OR, 2.06; 95% confidence interval, 1.68 to 2.53; $p < 0.001$) and for severely elevated compared with normal troponin (OR, 4.51; 95% confidence interval, 3.66 to 5.54; $p < 0.001$) independently of elevation in inflammatory markers. In conclusion, patients hospitalized with COVID-19 and elevated troponin had markedly increased mortality compared with patients with normal troponin levels. This risk was independent of cardiovascular co-morbidities and elevated markers of inflammation. **(Am J Cardiol 2020;00:1−7)**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus responsible for coronavirus disease 2019 (COVID-19), has rapidly spread across the globe, infecting millions of people and overwhelming health care systems. While COVID-19 primarily presents with pulmonary symptoms, markers of myocardial injury (i.e., elevated serum cardiac troponin serum) have been associated with increased mortality, particularly in patients with underlying cardiovascular disease.[1−5] However, these series were either small, single-centered, evaluated one troponin assay, or had a large proportion of patients still admitted without an endpoint at the time of analysis. Furthermore, it remains unclear if elevated troponin levels are due to ischemic myocardial injury via atherosclerotic plaque rupture or coronary thrombotic events (type 1 myocardial infarction), indirect injury associated with and sepsis resulting in supply-demand mismatch (type 2 myocardial infarction), or a direct result of the inflammatory surge frequently observed in patients hospitalized with COVID-19.[6] In this study, we further explored the relationship of elevated troponin levels with mortality, acute phase and inflammatory markers, and electrocardiogram evidence of acute myocardial infarction (AMI) in patients admitted with COVID-19 to the largest academic health system in New York State.

Methods

We conducted this study at hospitals within the Northwell Health system, which serves approximately 11 million people in New York. We included all consecutive patients 18 years or older who were (1) admitted to any of 13

[a]Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Northwell Health, Hempstead, New York; [b]Department of Cardiology, North Shore University Hospital, Manhasset, New York; [c]Department of Cardiology, Southside Hospital, Bay Shore, New York; [d]Division of Kidney Diseases and Hypertension, Department of Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Great Neck, New York; [e]Institute of Health Innovations and Outcomes Research, Feinstein Institutes for Medical Research, Manhasset, New York; and [f]Department of Information Services, Northwell Health, New Hyde Park, New York. Manuscript received July 31, 2020; revised manuscript received and accepted September 30, 2020.

Role of the Funding Sources: This work was supported by grants R24AG064191 from the National Institute on Aging of the National Institutes of Health and R01LM012836 from the National Library of Medicine of the National Institutes of Health. Neither of the funding sources had any role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. The views expressed in this paper are those of the authors and do not represent the views of the National Institutes of Health, the United States Department of Health and Human Services, or any other government entity. The corresponding author confirms that he had full access to all the data in the study and final responsibility for the decision to submit for publication.

See page 6 for disclosure information.

*Corresponding author: Tel: (516) 562-1428; fax: (516) 562-3992.
E-mail address: dmajure@northwell.edu (D.T. Majure).

0002-9149/
https://doi.org/10.1016/j.amjcard.2020.09.060

Northwell Health hospitals between March 1, 2020, and April 27, 2020, (2) had a SARS-CoV-2 virus infection confirmed by polymerase chain reaction testing of a nasopharyngeal sample, and (3) had an assessment of serum troponin measured within 48 hours of admission. We excluded patients with chronic kidney disease and end-stage renal disease identified based on the International Classification of Disease-10 codes at the time of admission, given the potential for elevated troponin due to impaired renal clearance independent of myocardial injury.[7,8] We extracted data on April 30, 2020, and censored all data on patients still admitted at that time. The Northwell Health Institutional Review Board approved this study as minimal risk using data collected for routine clinical practice and waived informed consent.

Four unique serum troponin assays are used across the Northwell Health system: cardiac troponin I with 99th percentile upper reference limit (URL) of 0.045 ng/ml (Siemens Dimension Vista Cardiac Troponin, Siemens Diagnostics, Tarrytown, New York); cardiac troponin I with URL of 0.056 ng/ml (Siemens Dimension EXL Systems, Siemens Diagnostics, Tarrytown, New York); cardiac troponin T with URL of 0.01 ng/ml (Roche Troponin T STAT, 4th generation, Roche Diagnostics, Basel, Switzerland); and high-sensitivity cardiac troponin T with URL of 19 ng/l (Elecys Troponin T Gen 5 STAT, Roche Diagnostics, Basel, Switzerland) To compare across grouped troponin assays, we normalized values to the 99th percentile URL of each individual assay and presented the results as ratios. We further categorized troponin ratios as normal ($\leq$1$\times$ URL), mildly elevated (>1 to $\leq$3$\times$ URL), and severely elevated (>3$\times$ URL).

We obtained covariates from the electronic medical record (Sunrise Clinical Manager, Allscripts, Chicago, Illinois) and included patient demographics, home medications, and laboratory tests obtained during the hospitalization. We identified co-morbidities based on the International Classification of Disease-10 codes at the time of admission. We defined initial laboratory testing as the first test result available within 48 hours of admission. The electrocardiogram reports were queried for keywords "acute MI," "myocardial infarction," "STEMI," "ischemia," and "ST elevation." Two independent cardiologists, blinded to troponin groups, reviewed and validated the electrocardiograms categorized as meeting electrocardiogram criteria for ST elevation AMI.

The primary outcome was in-hospital mortality. Secondary outcomes included percent of patients admitted to an intensive care unit (ICU), percent of patients requiring invasive mechanical ventilation, length of stay (LOS), and frequency of use of intravenous vasopressor and inotropic medications. We compared baseline characteristics across the 3 troponin groups. We compared categorical data using chi-square tests and continuous variables using the Kruskal-Wallis test. We used logistic regression to calculate odds ratios (ORs) of death stratified by troponin group.[9] For the model, we initially included variables with biologic plausibility and/or statistical significance in the univariate model. We adjusted for acute phase and inflammatory markers, including C-reactive protein, ferritin, procalcitonin, interleukin-6, D-dimer, and lactate dehydrogenase. We normalized each marker to the URL of the individual assay and categorized patients by no elevation ($\leq$1$\times$ URL), mild elevation in at least one marker of inflammation (>1 to $\leq$3$\times$ URL), and severe elevation in at least one marker of inflammation (>3$\times$ URL). Analyses were performed using Stata 12.1 (College Station, Texas).

Results

A total of 11,159 patients were admitted with COVID-19 during the study period. After excluding patients with chronic kidney disease and end-stage renal disease, and without troponin assessment, 6,247 (56%) patients had an assessment of troponin within 48 hours of admission, forming the primary population for analysis (Figure 1). Comparisons of patients who had an initial assessment of troponin within 48 hours versus those who did not are described in the supplemental materials (Supplementary Tables 1−3).

A total of 4,426 patients (71%) had normal troponin, 919 (15%) had mild elevation, and 902 (14%) had severe elevation in troponin levels. There were significant differences in baseline characteristics between the different troponin groups. Patients with elevated troponin were older than those with normal troponin ($p < 0.001$ for mildly elevated vs normal troponin, and for severely elevated troponin vs normal). Most patients were male, who were more likely to have mildly and severely elevated troponin than females ($p = 0.02$). Patients who identified as White and Black comprised 37% and 20% of the study population, respectively. A greater proportion of both White and Black patients had mildly (44% and 25%, respectively) and severely (45% and 23%, respectively) elevated troponin levels than patients who identified as Other or Multiracial ($p < 0.001$). In addition, similar proportions of White and Black patients had severely elevated troponin, with 16% of White patients and 17% of Black patients having troponin levels >3 times the URL. In contrast, patients who identified as Hispanic were less likely to have mildly and severely elevated troponin than non-Hispanic patients ($p < 0.0001$; Table 1).

Most patients had cardiovascular disease (CVD), defined as previous history of hypertension, coronary artery disease, peripheral vascular disease and/or heart failure; 63% of patients had at least 1, 17% had at least 2, and 3% had at least 3 cardiovascular co-morbidities. Most hospitalized patients had hypertension, which was more prevalent in patients with mildly and severely elevated troponin than normal troponin ($p < 0.001$ for comparison among groups). Patients with mildly and severely elevated troponin had a greater burden of CVD than patients with normal troponin for each comorbidity evaluated ($p < 0.001$). Notably, although only 9% of patients had a history of congestive heart failure, 35% of these patients had severely elevated troponin. In patients with severely elevated troponin, 21% had a history of congestive heart failure.

Among the 3 groups, there was a consistent and significant increase in the degree of elevated acute phase and inflammatory markers for each increase in troponin level. Compared with patients with normal troponin, patients with severely elevated troponin had a 29% higher level of C-reactive protein, 170% higher level of D-dimer, and 250% higher level of procalcitonin within 48 hours of admission.

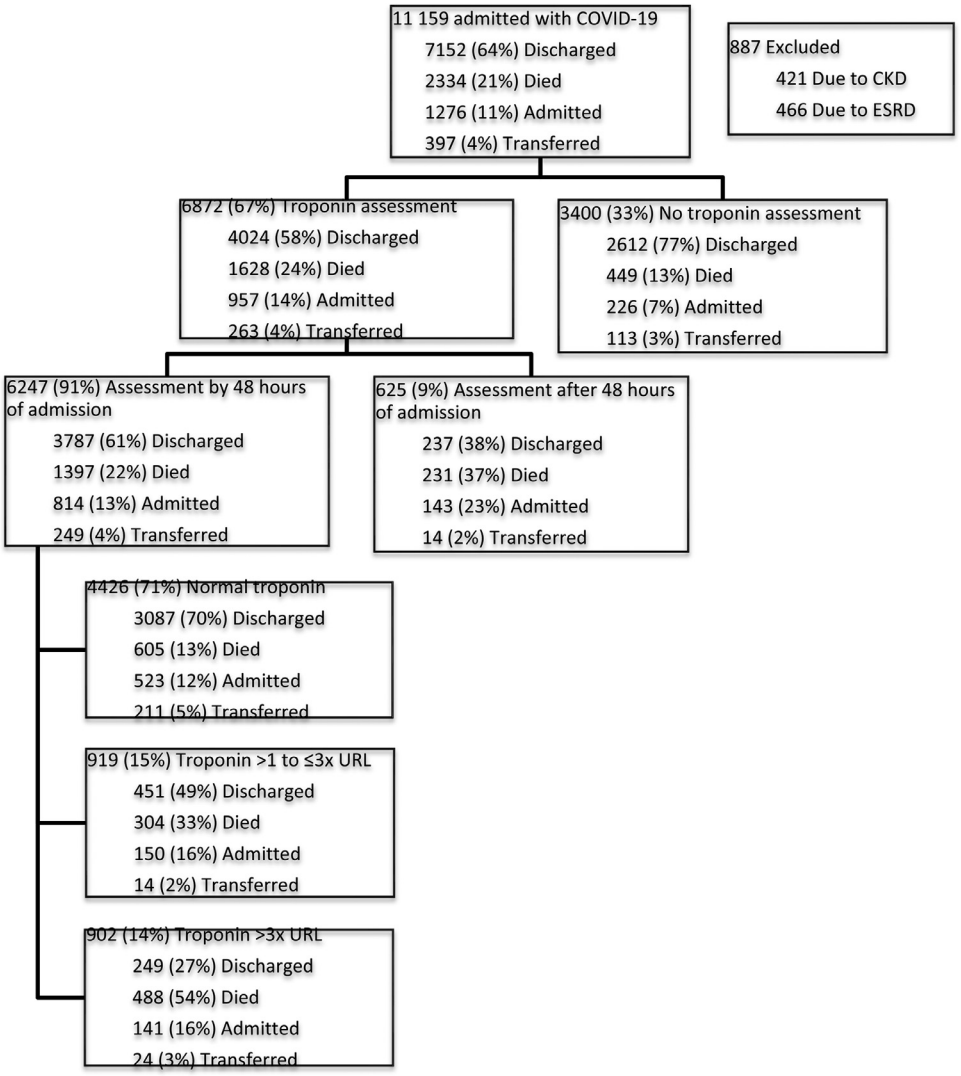

Figure 1. Flow diagram of patients admitted with COVID-19 and assessment of troponin.

In addition, markers of coagulopathy (international normalized ratio, prothrombin time, lactate dehydrogenase) were more abnormal in patients with mildly and severely elevated troponin than normal troponin, with the exception of activated partial thromboplastin time ($p = 0.79$; Table 1).

At least 1 electrocardiogram within 48 hours of admission was performed in 5,701 (91%) patients. Interestingly, few patients met electrocardiogram criteria for AMI. Specifically, 10 (0.2%) patients in the normal troponin group, 8 (0.9%) in the mildly elevated group, and 21 (2.3%) patients in the severely elevated group had at least 1 electrocardiogram with criteria for AMI ($p < 0.001$ for comparison among groups).

Although 30% of all patients were admitted to an ICU, 48% of those had severely elevated troponin levels. In addition, patients with mildly and severely elevated troponin levels were significantly more likely to require mechanical ventilation and more often required vasopressors than those with normal troponin levels. Only 1% of the study population received inotropes during the hospitalization, yet 2% of patients with mildly elevated troponin and 5% of patients with severely elevated troponin received inotropic support (Table 2).

Median LOS from admission was 6.2 days (interquartile range [IQR], 3.3 to 11.5), and patients with mildly elevated troponin had a significantly longer LOS than patients with normal troponin (7.2 days [IQR, 4.2 to 12.2] vs 6.1 days [IQR, 3.3 to 11.0]; $p = 0.005$). In contrast, there was no significant difference in LOS between patients with severely elevated (6.0 days [IQR, 2.8 to 11.6]) and normal troponin ($p = 0.438$). At the time of data collection, 814 (13%) patients were still hospitalized. Of these patients, a significantly greater percentage of patients had severely elevated troponin (12% had normal, 16% had mildly elevated, and 16% had severely elevated troponin; $p = 0.016$ among group comparison) (Table 2). A total of 1,397 (22%) patients died during hospitalization. Survival in patients with elevated troponin, mild or severe, was significantly lower than in patients with normal troponin. There were 605 (13%) deaths in patients with normal troponin, 304 (33%) in patients with mildly elevated troponin, and 488 (54%) in patients with severely elevated troponin. The

Table 1
Baseline characteristics of patients with serum troponin measurement within 48 hours of presentation

Variable	All patients (n = 6,247)	Troponin level (URL)			p Value
		Normal (n = 4,426)	>1 to ≤3× (n = 919)	>3× (n = 902)	
Age (years) (median (IQR))	66 (56-77)	62 (53-73)	75 (65-84)	77 (66-85)	<0.001
<60	2,084 (33%)	1,823 (41%)	137 (15%)	124 (14%)	<0.001
60-75	2,218 (36%)	1,637 (37%)	319 (35%)	262 (29%)	
≥75	1,945 (31%)	966 (22%)	463 (50%)	516 (57%)	
Sex					
Female	2,507 (40%)	1,824 (41%)	350 (38%)	333 (37%)	0.022
Male	3,740 (60%)	2,602 (59%)	569 (62%)	569 (63%)	
Race*					<0.001
White	2,455 (39%)	1,645 (37%)	408 (45%)	402 (45%)	
Black	1,254 (20%)	811 (18%)	233 (25%)	210 (23%)	
Asian	531 (8%)	401 (9%)	58 (6%)	72 (8%)	
Other	1,720 (28%)	1,367 (31%)	176 (19%)	177 (20%)	
Unknown	287 (5%)	202 (5%)	44 (5%)	41 (4%)	
Hispanic	1,352 (22%)	1,101 (25%)	129 (14%)	122 (14%)	<0.001
Not Hispanic	4,474 (71%)	3,004 (68%)	747 (81%)	723 (80%)	
Other/unknown	421 (7%)	321 (7%)	43 (5%)	57 (6%)	
BMI (Kg/m^2) (median (IQR)) (n = 4,918)	28 (25-33)	29 (26-33)	28 (24-32)	27 (23-32)	<0.001
Smoker					<0.001
Never	4,461 (71%)	3,348 (76%)	590 (64%)	523 (58%)	
Hypertension	3,717 (60%)	2,427 (55%)	666 (73%)	624 (69%)	<0.001
Coronary artery disease	833 (13%)	470 (11%)	180 (20%)	183 (20%)	<0.001
Heart failure	529 (9%)	200 (5%)	143 (16%)	186 (21%)	<0.001
Peripheral vascular disease	139 (2%)	68 (2%)	29 (3%)	42 (5%)	<0.001
Diabetes mellitus†	2,248 (36%)	1,479 (33%)	383 (42%)	386 (43%)	<0.001
Chronic obstructive pulmonary disease	399 (6%)	243 (6%)	77 (8%)	79 (9%)	<0.001
Asthma	551 (9%)	442 (10%)	64 (7%)	45 (5%)	<0.001
Chronic liver disease	138 (2%)	95 (2%)	25 (3%)	18 (2%)	0.501
Cancer	462 (7%)	286 (7%)	96 (11%)	80 (9%)	<0.001
Medications (n = 5627)					
Angiotensin-converting enzyme inhibitor	804 (14%)	547 (13%)	125 (15%)	132 (18%)	0.004
Angiotensin receptor blocker	1,054 (19%)	702 (17%)	207 (25%)	145 (20%)	<0.001
Either	1,853 (33%)	1,246 (31%)	331 (40%)	276 (38%)	<0.001
Systolic blood pressure (mm Hg)	129 (114-145)	129 (116-144)	128 (113-146)	129 (109-150)	0.182
Diastolic blood pressure (mm Hg)	76 (67-84)	76 (68-84)	74 (63-83)	73 (62-84)	<0.001
Heart rate (beats per minute)	98 (85-111)	98 (86-111)	96 (80-109)	98 (85-116)	<0.001
Respiratory rate (breaths per minute)	20 (18-24)	20 (18-24)	20 (18-24)	22 (18-26)	<0.001
White blood cell count ($x \times 10^9$/L)	7.6 (5.6-10.4)	7.3 (5.4-9.8)	7.9 (5.8-11.1)	9.5 (7-13.2)	<0.001
Lymphocytes ($\times 10^9$/L)	0.89 (0.62-1.25)	0.91 (0.65-1.24)	0.84 (0.58-1.22)	0.86 (0.55-1.28)	<0.001
Neutrophils ($\times 10^9$/L)	6.0 (4.1-8.7)	5.6 (4.0-8.0)	6.2 (4.3-9.2)	7.7 (5.6-11.0)	<0.001
Hemoglobin (g/dl)	13.3 (12.1-14.5)	13.5 (12.3-14.6)	12.9 (11.7-14.3)	12.6 (11.0-14.1)	<0.001
C-reactive protein (mg/dl)	11.3 (5.9-18.9)	10.8 (5.7-17.8)	11.3 (5.7-20.1)	13.9 (7.6-23.6)	<0.001
No.	5206	3709	750	747	
Ferritin (ng/ml)	785 (405-1422)	775 (394-1379)	799 (410-1433)	862 (453-1698)	<0.001
No.	5137	3648	753	736	
Interleukin-6	4 (1-5)	4 (1-5)	3.5 (1-5)	3 (1-5)	0.712
No.	383	264	46	73	
D-dimer (ng/ml)	471 (277-1034)	395 (249-726)	618 (350-1722)	1076 (548-3701)	<0.001
No.	4443	3120	683	640	
Procalcitonin (ng/ml)	0.20 (0.10-0.51)	0.16 (0.09-0.36)	0.29 (0.13-0.74)	0.56 (0.24-1.88)	<0.001
No.	4894	3466	662	595	
Lactate dehydrogenase (U/L)	419 (310-571)	398 (297-531)	441 (325-599)	548 (390-736)	<0.001
No.	4345	3124	591	630	
INR	1.19 (1.10-1.31)	1.18 (1.10-1.28)	1.19 (1.09-1.33)	1.24 (1.13-1.43)	<0.001
Prothrombin (seconds)	13.5 (12.5-14.9)	13.4 (12.5-14.6)	13.6 (12.4-15.2)	14.1 (12.8-16.3)	<0.001
aPTT (seconds)	31.4 (29.0-34.4)	31.4 (29.2-34.1)	31.4 (28.4-35.0)	31.2 (28.4-35.7)	0.794
Blood urea nitrogen (mg/dl)	18 (12-29)	15 (11-22)	26 (18-41)	36 (22-62)	<0.001
Serum creatinine (mg/dl)	1.1 (0.8-1.4)	1.0 (0.8-1.2)	1.3 (1.0-1.8)	1.7 (1.1-2.7)	<0.001
Aspartate aminotransferase (U/L)	48 (33-74)	47 (32-70)	47 (32-77)	58 (38-93)	<0.001
Alanine aminotransferase (U/L)	35 (22-57)	36 (23-59)	30 (19-49)	34 (20-56)	<.001
Creatine kinase (U/L)	171 (83-397)	146 (75-306)	212 (94-534)	282 (124-729)	<0.001
Lactate (mmol/L)	1.6 (1.2-2.3)	1.5 (1.2-2.1)	1.8 (1.3-2.7)	2.4 (1.6-3.7)	<0.001

aPTT = activated partial thromoplastin time; BMI = body mass index; INR = international normalized ratio; IQR = interquartile range; and URL = upper reference limit.

* Race and ethnicity data were collected by self-report in prespecified, fixed categories. Comorbidities were defined as medical diagnoses included in the medical history by ICD-10 coding.

† Assessed based on a diagnosis of diabetes mellitus and includes diet-controlled and non-insulin-dependent diabetes.

Table 2
Outcomes by troponin groups

Variable	Troponin Level (URL)				p Value
	All patients (n = 6,247)	Normal (n = 4,426)	>1 to ≤3× (n = 919)	>3× URL (n = 902)	
Primary Outcome					
Died	1,397 (22%)	605 (14%)	304 (33%)	488 (54%)	<0.001
Secondary Outcomes					
ICU admission	1,888 (30%)	1,142 (26%)	316 (35%)	430 (48%)	<0.001
Mechanical ventilation	1,456 (23%)	846 (19%)	254 (28%)	356 (40%)	<0.001
Length of stay (days) (median (IQR))	6.2 (3.3-11.5)	6.1 (3.3-11.0)	7.2 (4.2-12.2)*	6.0 (2.8-11.6)*	<0.001
Medications†					
Vasopressors	1,476 (24%)	833 (18%)	263 (29%)	380 (42%)	<0.001
Inotropes	85 (1%)	25 (1%)	14 (2%)	46 (5%)	<0.001

ICU = intensive care unit; IQR = interquartile range; and URL = upper reference limit.

* p = 0.005 for comparison of mildly elevated troponin compared to normal and p = 0.438 for comparison of severely elevated troponin compared to normal by pairwise comparison of means with equal variances.

† Any use of vasopressors or inotropes during admission. Vasopressors included dopamine, phenylephrine, epinephrine, norepinephrine, and vasopressin. Inotropes included milrinone and dobutamine.

unadjusted OR for comparison of mildly elevated versus normal troponin was 3.12 (95% confidence interval [CI], 2.7 to 3.7; p < 00001) and for comparison of severely elevated versus normal troponin was 7.44 (95% CI, 6.37 to 8.71; p < 0.0001).

In multivariate logistic regression analysis, including covariates of age, sex, race, ethnicity, hypertension, coronary artery disease, heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, and diabetes, use of angiotensin converting enzyme inhibitor or angiotensin receptor blocker, alanine aminotransferase, and serum creatinine the OR for death in patients with mildly elevated troponin versus normal troponin was 2.06 (95% CI, 1.68 to 2.53; p < 0.001), and with severely elevated troponin versus normal troponin was 4.51 (95% CI, 3.66 to 5.54; p < 0.001). Increased risk of death was independently associated with age, male sex, history of diabetes mellitus, serum creatinine, and severe elevation in inflammatory markers (adjusted OR, 2.43; 95% CI, 1.41 to 4.21; p = 0.001; Figure 2). Milder elevation in inflammatory markers was not associated with risk of death (adjusted OR, 0.92; 95% CI, 0.69 to 1.21; p = 0.54). In general, point estimates of odds of death were similar between troponin assays, but variability between assays was observed (Figure 3). In sensitivity analyses, the association of increased mortality with both mildly and severely elevated troponin persisted even after excluding patients who were mechanically ventilated within the first day of admission. In addition, excluding patients with electrocardiogram criteria for AMI did not meaningfully change the OR for death in multivariate modeling (data not shown).

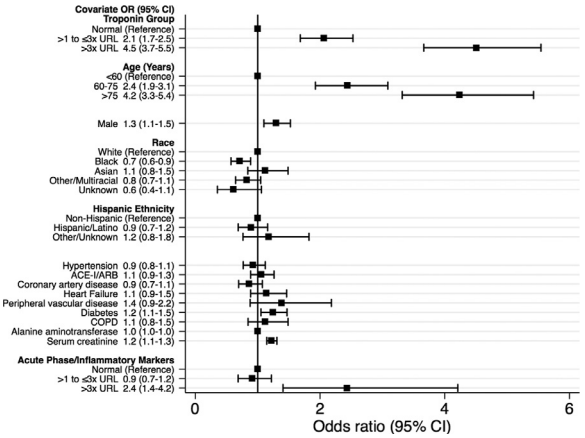

Figure 2. Forest plot of odds ratio of death in patients admitted with COVID-19. ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; CI = confidence interval; COPD, chronic obstructive pulmonary disease; OR = odds ratio; URL = upper reference limit.

Discussion

In the largest series to date evaluating the impact of myocardial injury in COVID-19, comprising 6,247 patients admitted with COVID-19 who had serum troponin levels assessed, we made the following observations: (1) patients with mildly or severely elevated troponin had a >two- and four-fold increase in the risk of death, respectively, than patients with normal troponin levels; (2) patients with elevated troponin were more often older, male, and had

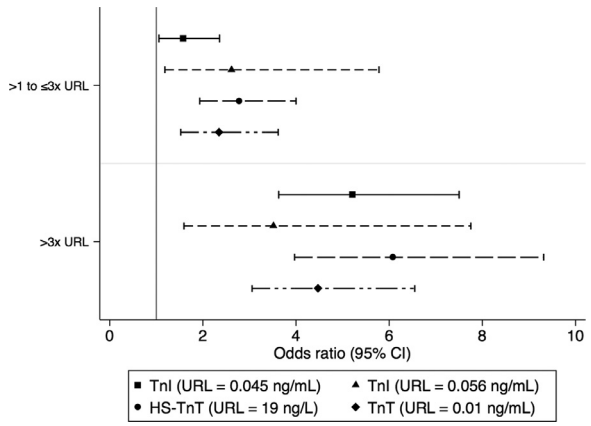

Figure 3. Forest plot of adjusted odds of mortality by troponin elevation stratified by troponin assay type. TnI = Troponin I; TnT = Troponin T; HS-TnT = high-sensitivity Troponin T; and URL = upper reference limit.

significantly more CVD than patients with normal troponin levels; (3) there was an incremental increase in acute phase and inflammatory markers that correlated with elevated troponin and outcomes; (4) patients with elevated troponin levels were frequently admitted to an ICU, required mechanical ventilation, and were treated with vasopressors; and (5) elevated troponin was an independent predictor of in-hospital mortality regardless of baseline CVD, electrocardiogram evidence of AMI, or the degree of elevated acute phase and inflammatory markers. We also demonstrated increased mortality with troponin levels across a range of troponin assays.

There is a growing body of data regarding the prevalence and impact of myocardial injury in patients hospitalized with COVID-19. Single-center studies in a small number of patients estimated myocardial injury to occur in approximately 20% of patients, ranging from 5% to 38%.[1−5] In our study, approximately 30% of patients who had troponin assessed within 48 hours of admission had evidence of at least mild myocardial injury, with 14% having severe myocardial injury as reflected by an elevation in troponin >3 times the URL. The true incidence of myocardial injury in hospitalized patients is likely lower, as 40% of patients did not have troponin assessed, and mortality in these patients was less than in those who had troponin assessed (17% vs 20%, respectively; $p < 0.001$) (Supplemental Table 3).

Multiple mechanisms of myocardial injury may be associated with COVID-19, including injury related to inflammation and cytokine storm, direct viral-mediated injury, hypoxic respiratory failure, downregulation of ACE2 receptors, hypercoagulability, diffuse myocardial endothelial injury, and acute plaque rupture.[6,10,11] Although we did not measure changes in troponin over time, elevations in troponin likely reflected imbalance between myocardial oxygen supply and demand.[12] However, direct myocardial involvement cannot be excluded and myocarditis associated with COVID-19 remains poorly defined.[11,13]

Electrocardiographic criteria for AMI was infrequent, and excluding these patients from our analysis did not change the risk associated with elevated troponin. However, given the known risk of thromboembolic events in patients hospitalized with COVID-19,[14−16] undiagnosed coronary thrombotic events may have occurred. Importantly, controlling for the degree of inflammation did not attenuate the risk associated with increased troponin, although only severely, and not mildly, elevated inflammatory markers were independently associated with an increased risk of death. These findings suggest that inflammation alone cannot account for the myocardial injury and the associated increase in mortality.

As reported in earlier studies,[1−3] a previous history of CVD was common in patients admitted with COVID-19, and the burden of CVD was more prevalent in patients with mildly and severely elevated troponin. However, in multivariate regression, CVD did not independently predict survival, with the exception of diabetes mellitus, a known risk factor for poor outcomes with COVID-19.[17] The incidence of myocardial injury increased with age and was disproportionately associated with male sex.

This retrospective observational study has several limitations. Not all patients had troponin assessments, which may impact the strength of the association between troponin and mortality. Some covariates, such as body mass index, could not be calculated for the entire cohort of patients and were not included in multivariate modelling. A lack of complete assessment of inflammatory and acute phase markers limited our ability to draw definitive conclusions regarding the association of myocardial injury with the inflammatory state seen in COVID-19. Follow-up data for patients discharged alive were not available, and survival estimates were limited to data collected during the hospitalization.

In conclusion, we observed that patients hospitalized with COVID-19 and elevated troponin had a significant increase in the risk of death, and that patients with severely elevated troponin fared worse than those with mildly elevated troponin. The risk of death was independent of CVD and elevated acute phase and inflammatory markers, but it was not associated with electrocardiogram evidence of AMI. Patients admitted with COVID-19 should have an assessment of troponin to assist in risk stratification and to identify patients who may need further evaluation and escalation of care. Further research is needed to fully understand the mechanisms of myocardial injury in patients with COVID-19.

Disclosures

The authors report no real or apparent conflicts of interest. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

David T. Majure: Conceptualization, Methodology, Validation, Formal analysis, Writing − Original Draft, Writing − Review & Editing. **Luis Gruberg**: Conceptualization, Writing − Review & Editing. **Shahryar G. Saba**: Conceptualization, Writing − Review & Editing. **Charlotte Kvasnovsky**: Conceptualization, Methodology, Validation, Formal analysis. **Jamie S. Hirsch**: Conceptualization, Validation, Resources, Data Curation. **Rajiv Jauhar**, MD: Conceptualization, Writing − Review & Editing

Acknowledgments

The Northwell Health COVID-19 Research Consortium: Bani M. Azari, MD, PhD; Saurav Chatterjee, MD; Stuart L. Cohen, MD; Jennifer Cookingham, MHA; Arvind Reddy Devanabanda, MD; Crystal Herron, PhD; Asma Khaliq, MD; Angela Li, MD; Alex Makhnevich, MD; Perwaiz M. Meraj, MD; Ernesto P. Molmenti, MD, PhD, MBA; Pey-Jen Yu, MD.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.09.060.

1. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, Wang H, Wan J, Wang X, Lu Z. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;5:1–8.
2. Shi S, Qin M, Shen B, Cai Y, Liu T, Yang F, Gong W, Liu X, Liang J, Zhao Q, Huang H, Yang B, Huang C. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020;5:802–810.
3. Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, Zhao S, Somani S, Van Vleck T, Vaid A, Chaudhry F, De Freitas JK, Fayad ZA, Pinney SP, Levin M, Charney A, Bagiella E, Narula J, Glicksberg BS, Nadkarni G, Mancini DM, Fuster V, Mount Sinai Covid Informatics C. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. *J Am Coll Cardiol* 2020. [Epub ahead of print].
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395:497–506.
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061–1069.
6. Clerkin KJ, Fried JA, Raikhelkar J, Sayer G, Griffin JM, Masoumi A, Jain SS, Burkhoff D, Kumaraiah D, Rabbani L, Schwartz A, Uriel N. Coronavirus disease 2019 (COVID-19) and cardiovascular disease. *Circulation* 2020;141:1648–1655.
7. deFilippi C, Seliger SL, Kelley W, Duh SH, Hise M, Christenson RH, Wolf M, Gaggin H, Januzzi J. Interpreting cardiac troponin results from high-sensitivity assays in chronic kidney disease without acute coronary syndrome. *Clin Chem* 2012;58:1342–1351.
8. Parikh RH, Seliger SL, de Lemos J, Nambi V, Christenson R, Ayers C, Sun W, Gottdiener JS, Kuller LH, Ballantyne C, deFilippi CR. Prognostic significance of high-sensitivity cardiac troponin T concentrations between the limit of blank and limit of detection in community-dwelling adults: a metaanalysis. *Clin Chem* 2015;61:1524–1531.
9. Schoenfeld D. Survival methods, including those using competing risk analysis, are not appropriate for intensive care unit outcome studies. *Crit Care* 2006;10:103.
10. Chapman AR, Bularga A, Mills NL. High-sensitivity cardiac troponin can be an ally in the fight against COVID-19. *Circulation* 2020;141:1733–1735.
11. Imazio M, Klingel K, Kindermann I, Brucato A, De Rosa FG, Adler Y, De Ferrari GM. COVID-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis? *Heart* 2020. [Epub ahead of print].
12. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD, Executive Group on behalf of the Joint European Society of Cardiology /American College of Cardiology /American Heart Association /World Heart Federation Task Force for the Universal Definition of Myocardial I. Fourth universal definition of myocardial infarction (2018). *Circulation* 2018;138:e618–e651.
13. Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, Sepe PA, Resasco T, Camporotondo R, Bruno R, Baldanti F, Paolucci S, Pelenghi S, Iotti GA, Mojoli F, Arbustini E. Myocardial localization of coronavirus in COVID-19 cardiogenic shock. *Eur J Heart Fail* 2020;22:911–915.
14. Klok FA, Kruip M, van der Meer NJM, Arbous MS, Gommers D, Kant KM, Kaptein FHJ, van Paassen J, Stals MAM, Huisman MV, Endeman H. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res* 2020;191:145–147.
15. Llitjos JF, Leclerc M, Chochois C, Monsallier JM, Ramakers M, Auvray M, Merouani K. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost* 2020;18:1743–1746.
16. Middeldorp S, Coppens M, van Haaps TF, Foppen M, Vlaar AP, Muller MCA, Bouman CCS, Beenen LFM, Kootte RS, Heijmans J, Smits LP, Bonta PI, van Es N. Incidence of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020. [Epub ahead of print].
17. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, Qin R, Wang H, Shen Y, Du K, Zhao L, Fan H, Luo S, Hu D. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev* 2020:e3319.