JAMA Cardiology | Brief Report

Association of Troponin Levels With Mortality in Italian Patients Hospitalized With Coronavirus Disease 2019
Results of a Multicenter Study

Carlo Mario Lombardi, MD; Valentina Carubelli, MD, PhD; Annamaria Iorio, MD; Riccardo M. Inciardi, MD; Antonio Bellasi, MD, PhD; Claudia Canale, MD; Rita Camporotondo, MD; Francesco Catagnano, MD; Laura A. Dalla Vecchia, MD; Stefano Giovinazzo, MD; Gloria Maccagni, MD; Massimo Mapelli, MD; Davide Margonato, MD; Luca Monzo, MD, PhD; Vincenzo Nuzzi, MD; Chiara Oriecuia, MSc; Giulia Peveri, MSc; Andrea Pozzi, MD; Giovanni Provenzale, MD; Filippo Sarullo, MD; Daniela Tomasoni, MD; Pietro Ameri, MD, PhD; Massimiliano Gnecchi, MD, PhD; Sergio Leonardi, MD, MHS; Marco Merlo, MD; Piergiuseppe Agostoni, MD, PhD; Stefano Carugo, MD; Gian Battista Danzi, MD; Marco Guazzi, MD, PhD; Maria Teresa La Rovere, MD; Andrea Mortara, MD; Massimo Piepoli, MD, PhD; Italo Porto, MD, PhD; Gianfranco Sinagra, MD; Maurizio Volterrani, MD, PhD; Claudia Specchia, PhD; Marco Metra, MD; Michele Senni, MD

IMPORTANCE Myocardial injury, detected by elevated plasma troponin levels, has been associated with mortality in patients hospitalized with coronavirus disease 2019 (COVID-19). However, the initial data were reported from single-center or 2-center studies in Chinese populations. Compared with these patients, European and US patients are older, with more comorbidities and higher mortality rates.

OBJECTIVE To evaluate the prevalence and prognostic value of myocardial injury, detected by elevated plasma troponin levels, in a large population of White Italian patients with COVID-19.

DESIGN, SETTING, AND PARTICIPANTS This is a multicenter, cross-sectional study enrolling consecutive patients with laboratory-confirmed COVID-19 who were hospitalized in 13 Italian cardiology units from March 1 to April 9, 2020. Patients admitted for acute coronary syndrome were excluded. Elevated troponin levels were defined as values greater than the 99th percentile of normal values.

MAIN OUTCOMES AND MEASURES Clinical characteristics and outcomes stratified as elevated or normal cardiac troponin levels at admission, defined as troponin T or troponin I at a level greater than the 99th percentile of normal values.

RESULTS A total of 614 patients with COVID-19 were included in this study (mean age [SD], 67 [13] years; 70.8% male), of whom 148 patients (24.1%) died during the hospitalization. Elevated troponin levels were found in 278 patients (45.3%). These patients were older (mean [SD] age, 64.0 [13.6] years vs 71.3 [12.0] years; $P < .001$) and had higher prevalence of hypertension (168 patients [50.5%] vs 182 patients [65.9%]; $P < .001$), heart failure (24 [7.2%]; 63 [22.8%]; $P < .001$), coronary artery disease (50 [15.0%] vs 87 [31.5%]; $P < .001$), and atrial fibrillation (33 [9.9%] vs 67 [24.3%]; $P < .001$). Elevated troponin levels were associated with an increased in-hospital mortality (37% vs 13%; HR, 1.71 [95% CI, 1.13-2.59]; $P = .01$ via multivariable Cox regression analysis), and this was independent from concomitant cardiac disease. Elevated troponin levels were also associated with a higher risk of in-hospital complications: heart failure (44 patients [19.2%] vs 7 patients [2.9%]; $P < .001$), sepsis (31 [11.7%] vs 21 [6.4%]; $P = .03$), acute kidney failure (41 [20.8%] vs 13 [6.2%]; $P < .001$), multiorgan failure (21 [10.9%] vs 6 [2.9%]; $P = .003$), pulmonary embolism (27 [9.9%] vs 17 [5.2%]; $P = .04$), delirium (13 [6.8%] vs 3 [1.5%]; $P = .02$), and major bleeding (16 [7.0%] vs 4 [1.6%]; $P = .008$).

CONCLUSIONS AND RELEVANCE In this multicenter, cross-sectional study of Italian patients with COVID-19, elevated troponin was an independent variable associated with in-hospital mortality and a greater risk of cardiovascular and noncardiovascular complications during a hospitalization for COVID-19.

JAMA Cardiol. 2020;5(11):1274-1280. doi:10.1001/jamacardio.2020.3538
Published online August 26, 2020.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Marco Metra, MD, Department of Cardiology, ASST Spedali Civili di Brescia, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Piazza Spedali Civili 1, 25123 Brescia, Italy (metramarco@libero.it).

Troponin levels are a well-established marker of myocardial injury.[1] Early studies[2-5] in patients with coronavirus disease 2019 (COVID-19) have demonstrated that elevated plasma troponin levels were common and associated with a more severe clinical course and higher mortality. However, these studies were mostly based on Chinese patients, were limited to 1 or 2 centers, and/or had a small sample size.[2-5] Since COVID-19 reports from other countries are characterized by an older patient age, more comorbidities, and higher risk of death than those from China,[6-8] the importance of elevated troponin levels in non-Chinese populations needs further investigation.

In Italy, the COVID-19 outbreak caused a major reorganization of the health care system in pandemic areas, with cardiology units admitting patients with COVID-19 almost exclusively, mostly those with associated cardiac disease.[6,8,9] The old age of and the high burden of comorbidities in Italian patients account for their higher risk of death and complications.[6,8] This population has therefore ideal characteristics to analyze the association of myocardial injury with the outcomes of patients with COVID-19. In this study, we investigated the prevalence and prognostic implications of myocardial injury, detected by elevated troponin levels, in consecutive patients with COVID-19 who were hospitalized in 13 cardiology units in Italy.

Key Points

Question Is myocardial injury, detected by troponin elevation, associated with mortality and higher cardiovascular and noncardiovascular complications in patients hospitalized with coronavirus disease 2019?

Findings In this multicenter, cross-sectional study of 614 White Italian patients hospitalized with coronavirus disease 2019, elevated troponin values were associated with higher mortality and a greater risk of cardiovascular and noncardiovascular complications.

Meaning In this study of patients with coronavirus disease 2019, elevated troponin levels on admission are associated with increased risk of in-hospital death and complications.

Methods

Study Population

This is a multicenter, cross-sectional study enrolling consecutive patients with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection who were referred to 13 Italian cardiology units from March 1 to April 9, 2020 (list of centers and investigators in the eAppendix in the Supplement). We included patients hospitalized with a laboratory-confirmed diagnosis of COVID-19 and high-sensitivity plasma troponin levels, either troponin I or troponin T, measured within 24 hours from the time of COVID-19 diagnosis. Patients hospitalized with a diagnosis of acute coronary syndrome were excluded.

Diagnoses of COVID-19 were made by real-time reverse transcriptase-polymerase chain reaction assays of nasal and pharyngeal swabs. Real-time reverse transcriptase-polymerase chain reaction assays of lower respiratory tract aspirates were also performed when indicated. Patients were followed up after the COVID-19 diagnosis, and all causes of in-hospital mortality or discharge were ascertained until April 23, 2020. This study complied with the Declaration of Helsinki and was approved by the ethical committee of Spedali Civili di Brescia, Brescia, Italy, and each recruiting center. This is a retrospective observational study. As such, a waiver for consent was granted by local ethics committees, provided the informed consent was collected at the follow-up visit for the patients who were still alive.

Patients' data were extracted from the in-hospital medical records. Cardiac injury was defined by plasma levels of high-sensitivity troponin, either troponin T or troponin I, greater than the 99th percentile of normal values, as per manufacturer indications.

Statistical Analysis

Data are presented stratified by troponin level at admission. Comparisons between 2 independent groups were made, respectively, using *t* tests for normally distributed continuous variables, Wilcoxon tests for nonnormally distributed ones, and χ^2 tests for proportions. For all variables with at least 1 expected count less than 5, Fisher exact tests instead of χ^2 tests were used. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline checklist for data reporting. Accordingly, we showed the number of nonmissing values for each variable.

Cumulative incidence functions of death were computed, taking into account hospital discharge as a competing event. Comparison of cumulative incidence functions among subgroups was performed by means of the Gray test. Variables clinically relevant and significantly associated with the risk of death at the univariable analysis were tested in a multiple Cox regression model to identify independent risk factors using a complete-case approach (ie, observations of participants with missing data were omitted). The hazard ratios (HRs), 95% CIs, and *P* values from a Wald test are reported. A 2-tailed *P* value less than .05 was considered statistically significant. Statistical analyses were performed using SAS statistical software version 9.4 (SAS Institute Inc).

Results

In this analysis, 614 patients were included (mean age [SD], 67 [13] years; 435 male patients [70.8%]), of whom 148 patients (24.1%) died during a median hospital stay of 13 (interquartile range, 8-23) days. Elevated troponin levels were found in 278 of the 614 patients studied (45.3%). Compared with those with normal values, patients with increased troponin levels were older (mean [SD] age, 64.0 [13.6] years vs 71.3 [12.0] years; $P < .001$), had higher prevalence of cardiac comorbidities (hypertension: 168 patients [50.5%] vs 182 patients [65.9%]; $P < .001$, heart failure: 24 [7.2%] vs 63 [22.8%]; $P < .001$; coronary artery disease: 50 [15.0%] vs 87 [31.5%]; $P < .001$; atrial

Table. Demographic and Clinical Characteristics of the Study Population at Admission Stratified by Baseline Troponin Level (N = 614)

Characteristic	Troponin				P value
	Normal (n = 336)		Elevated (n = 278)		
	No. Assessed	No. Affected (%)	No. Assessed	No. Affected (%)	
Age, mean (SD), y	336	64.0 (13.6)	278	71.3 (12.0)	<.001
Male	336	234 (69.6)	278	201 (72.3)	.53
BMI ≥30	262	51 (19.5)	213	46 (21.6)	.65
Smoker (ever)	292	78 (26.7)	224	73 (32.6)	.18
Hypertension	333	168 (50.5)	276	182 (65.9)	<.001
Dyslipidemia	333	71 (21.3)	275	106 (38.5)	<.001
Diabetes	333	66 (19.8)	276	82 (29.7)	.006
Heart failure	333	24 (7.2)	276	63 (22.8)	<.001
Atrial fibrillation	333	33 (9.9)	276	67 (24.3)	<.001
Coronary artery disease	333	50 (15.0)	276	87 (31.5)	<.001
Prior cardiac surgery or percutaneous valve treatment	333	27 (8.1)	276	39 (14.1)	.03
Prior heart transplant/LVAD	333	0 (0.0)	276	4 (1.4)	.09
COPD	333	27 (8.1)	276	31 (11.2)	.24
Chronic kidney disease with eGFR <60 mL/min/m^2	333	34 (10.2)	276	76 (27.5)	<.001
Prior ACEi or ARB therapy	312	110 (35.3)	259	114 (44.0)	.04
Prior anticoagulant therapy	309	29 (9.4)	254	55 (21.7)	<.001
Prior statin therapy	313	68 (21.7)	258	101 (39.1)	<.001
Temperature, mean (SD), °C	332	37.3 (1.0)	269	37.2 (1.0)	.40
Temperature ≥37.5 °C	332	151 (45.5)	269	111 (41.3)	.34
Respiratory rate ≥22 breaths/min	277	141 (50.9)	176	107 (60.8)	.049
Blood pressure, mean (SD), mm Hg					
Systolic	330	129 (20)	271	129 (24)	.97
Diastolic	330	75 (12)	271	73 (15)	.06
Heart rate, mean (SD), beats/min	328	86 (16)	272	87 (20)	.60
Oxygen saturation, ambient air, median (IQR), %	329	93 (88-96)	271	92 (87-96)	.03
Pao_2/FiO_2, median (IQR), mm Hg/%	298	246 (127-319)	238	233 (120-310)	.29
Pao_2/FiO_2 <300 mm Hg/%	298	207 (69.5)	238	170 (71.4)	.69
SOFA score					
Median (IQR)	194	2 (1-3)	188	3 (2-4)	<.001
≥3	194	70 (36.1)	188	103 (54.8)	<.001
≥6	194	9 (4.6)	188	24 (12.8)	.008
COVID-19 score peak, median (IQR)	64	4.5 (1.0-10.3)	104	10.0 (3.8-14.0)	<.001
LV ejection fraction, median (IQR), %	104	58.0 (53.8-61.0)	131	55.0 (40.0-58.0)	<.001

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; eGFR, estimated glomerular filtration rate; FiO_2, fraction of inspired oxygen; IQR, interquartile range; LV, left ventricular; LVAD, left ventricular assist device; Pao_2, oxygen partial pressure at arterial gas analysis; SOFA, sequential organ failure assessment.

fibrillation: 33 [9.9%] vs 67 [24.3%]; $P < .001$), had lower left ventricular ejection fraction (median [interquartile range], 58.0% [53.8%-61.0%] vs 55.0% [40.0%-58.0%]; $P < .001$), and were more likely to be treated with angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs) (110 patients [35.3%] vs 114 patients [44.0%]; $P = .04$), anticoagulants (29 patients [9.4%] vs 55 patients [21.7%]; $P < .001$), and statins (68 patients [21.7%] vs 101 patients [39.1%]; $P < .001$) (**Table**). Laboratory examinations (with values reported as median [interquartile ranges]) showed lower lymphocytes (973 [630-1400] cells/μL vs 880 [600-1140] cells/μL; $P = .008$ [to convert to cells × 10^9 per liter, multiply by 0.001]) and higher C-reactive protein (46 [13-118] mg/dL vs 70 [18-160] mg/dL; $P = .007$ [to convert to milligrams per liter, multiply by 10]), procalcitonin (0.13 [0.06-0.40] ng/mL; 0.30 [0.10-3.00] ng/mL; $P < .001$), D-dimer (789 [426-1699] μg/mL vs 1038 [496-3299] μg/mL; $P = .02$ [to convert to nanomoles per liter, multiply by 5.476]), creatinine (0.92 [0.75-1.11] mg/dL vs 1.12 [0.89-1.67] mg/dL; $P < .001$ [to convert to micromoles per liter, multiply by 88.4]), and N-terminal pro-brain natriuretic peptide (204 [85-554] pg/mL vs 882 [196-3170] pg/mL; $P < .001$) plasma levels in the patients with elevated troponin (eTable 1 in the Supplement). Factors associated with elevated troponin levels were estimated glomerular filtration rate (odds

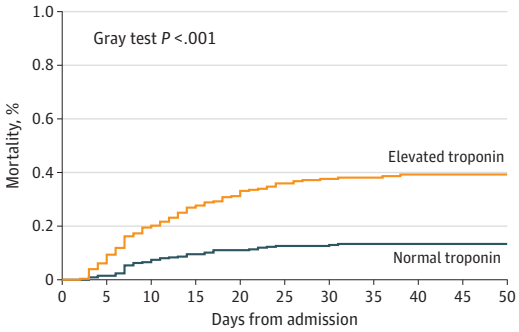
ratio [OR] per 10 mL/min, 0.82 [95% CI, 0.76-0.88]; *P* < .001), serum sodium (OR per 1 mEq/L, 1.06 [95% CI, 1.02-1.10]; *P* = .004 [to convert to millimoles per liter, multiply by 1.0]), C-reactive protein (OR per 1 mg/dL, 1.03 [95% CI, 1.01-1.05]; *P* = .002), a history of heart failure (OR, 2.01 [95% CI, 1.07-3.79]; *P* = .03), a history of coronary artery disease (OR, 2.04 [95% CI, 1.27-3.29]; *P* = .003), and prior anticoagulant therapy (OR, 2.01 [95% CI, 1.16-3.50]; *P* = .01) (eTable 2 in the Supplement).

Elevated Troponin Levels at the Time of Admission and In-Hospital Outcomes

Elevated serum troponin was associated with increased in-hospital death (104 events [37.4%] vs 44 events [13.1%]; *P* < .001; **Figure 1**; eTable 3 in the Supplement). The mortality rate was lowest in the patients with no history of cardiac disease and low troponin levels, intermediate in those with either preexisting cardiac disease (hazard ratios [HRs]: heart failure [HF], 3.49 [95% CI, 1.62-7.53]; coronary artery disease [CAD], 2.96 [95% CI, 1.57-5.58]; atrial fibrillation [AF], 3.59 [95% CI, 1.77-7.29]) or elevated troponin levels (HRs: HF, 3.27 [95% CI, 2.19-4.88]; CAD, 3.60 [95% CI, 2.34-5.55]; AF, 3.49 [95% CI, 2.32-5.24]), and highest in those with both elevated troponin levels and one of the major cardiac comorbidities (HRs: HF, 5.28 [95% CI, 3.25-8.58], CAD, 5.22 [95% CI, 3.22-8.47]; AF, 5.09 [95% CI, 3.09-8.36]) (**Figure 2**). The association of elevated troponin levels and mortality remained significant after adjustment for comorbidities (adjusted HR, 1.71 [95% CI, 1.13-2.59]; *P* = .01) (eTable 4 in the Supplement). Exploratory analyses were performed when the percentage of complete-case observations was less than 80% (eTables 5, 6, and 7 in the Supplement). The HRs associated with elevated level of troponin remained similar to the HRs estimated in the main analysis when adjusted for lymphocytes and respiratory rate (n = 334, adjusted HR, 1.65 [95% CI, 1.03-2.62]; *P* = .04) and prior ACEi or ARB therapy and prior statin therapy (n = 473; adjusted HR, 1.61 [95% CI, 1.05-2.47]; *P* = .03) and similar but nonsignificant when adjusted for lymphocytes, respiratory rate, prior ACEi or ARB therapy, and prior statin therapy (n = 299; adjusted HR, 1.50 [95% CI, 0.92-2.45]; *P* = .11).

Elevated troponin levels were also associated with a complicated clinical course. Significant differences between patients with increased vs those with normal troponin levels were found for sepsis (31 patients [11.7%] vs 21 patients [6.4%]; *P* = .03), acute kidney failure (41 [20.8%] vs 13 [6.2%]; *P* < .001), multiorgan failure (21 [10.9%] vs 6 [2.9%]; *P* = .003), pulmonary embolism (27 [9.9%] vs 17 [5.2%]; *P* = .04), delirium (13 [6.8%] vs 3 [1.5%]; *P* = .02), and major bleeding (16 [7.0%] vs 4 [1.6%]; *P* = .008), as well as heart failure (44 [19.2%] vs 7 [2.9%]; *P* < .001) and non-ST-elevation myocardial infarction (16 [7.0%] vs 1 [0.4%]; *P* < .001) (eTable 3 in the Supplement).

Figure 1. Cumulative Incidence of Death During Hospitalization Stratified by Baseline Troponin Level (N = 614)



No. at risk

Normal troponin	336	314	238	166	126	88	62	36	19	10	6
Elevated troponin	278	258	182	117	78	48	27	16	7	5	1

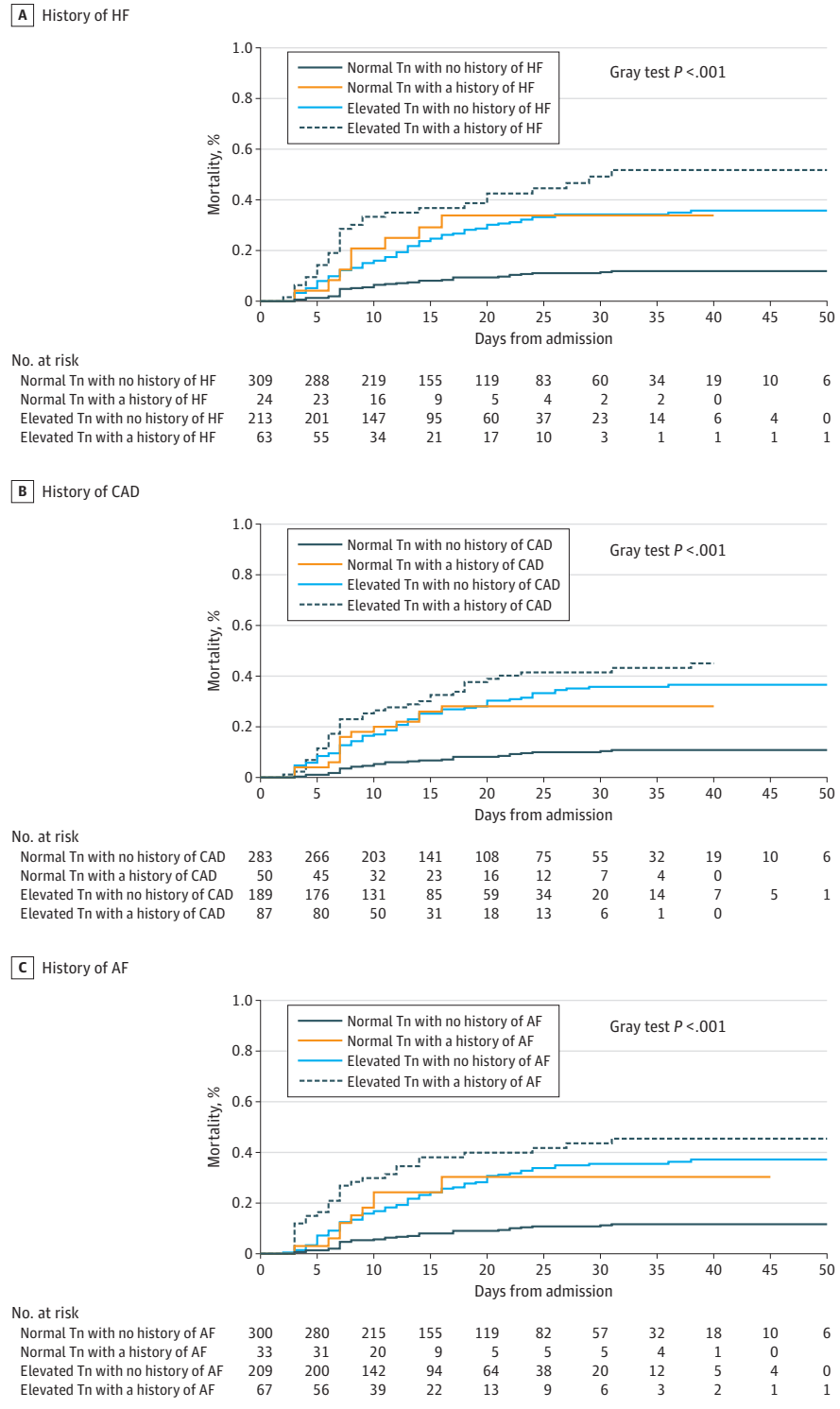
Discussion

Our results show that myocardial injury, detected by high troponin levels, is present in a high proportion of patients hospitalized for COVID-19 and independently associated with mortality and cardiovascular and noncardiovascular complications. Elevated troponin levels were found in 45.3% of the patients and were associated with a 71% increase in the risk of in-hospital death and with a more than 2-fold increase in major complications, including sepsis, acute kidney failure, multiorgan failure, pulmonary embolism, and major bleeding. The incidence of heart failure and non-ST-elevation acute myocardial infarction were more than 6-fold in the patients with increased troponin levels compared with others.

To our knowledge, this is the first report regarding the clinical significance of elevated troponin levels in a large, multicenter cohort of consecutive White Italian patients who were admitted for COVID-19. Our results confirm and expand those observed in smaller, mostly single-center studies from Chinese patients,[2-5] as well as the more diverse, multiethnic population of New York, New York.[10] Compared with these studies, the prevalence of elevated troponin levels in this population was higher. This can be explained by the older mean age and high prevalence of cardiac comorbidities of this patient group. Accordingly, kidney function, history of heart failure and coronary artery disease, and oral anticoagulation, a variable associated with a history of atrial fibrillation, were independently associated with elevated troponin levels by multivariable logistic regression analysis. The older age and higher prevalence of comorbidities, compared with the Chinese series, were consistent with the characteristics of patients with COVID-19 from Europe and the United States.[7-9]

The mechanisms underlying cardiac involvement in COVID-19 are multiple and not entirely clear.[11-14] They may include nonspecific mechanisms attributable to systemic infection, respiratory failure, and hypoxemia, as well as myocardial injury caused by the systemic inflammatory response.[11-14] It has been hypothesized that one of the pivotal consequences of COVID-19 is an abnormal immune host response.[12] Consistently, patients with myocardial injury have a more marked inflammatory response with higher C-reactive protein, D-dimer, fibrinogen, and procalcitonin levels in both this study and previous studies.[2,4] It may

Figure 2. Cumulative Incidence of Death During Hospitalization Stratified by Baseline Troponin Level and Histories of Heart Failure (HF) (A), Coronary Artery Disease (CAD) (B), Atrial Fibrillation (AF) (C) (n = 609)



Tn indicates troponin.

therefore be hypothesized that increased troponin levels are the expression of the involvement of different organs and tissues, such as can be expected in a general hyperinflammatory disorder.[12,14]

Our study provides new data that may be of clinical utility in managing patients with COVID-19. Measurement of troponin levels at the time of hospital admission for COVID-19 might be included in the diagnostic workup to

identify patients at increased risk of worse outcome and those who may require more intensive treatment. Whether the detection of myocardial injury is associated with abnormalities in cardiac structure and function has not been described. Only a small percentage of these patients underwent echocardiography, and their follow-up was too short to be able to determine whether troponin elevation had an association with cardiac function and postdischarge events, including heart failure.

Limitations

The main limitation of our study is the analytic accuracy of the prognosticative value of troponin, given the different assays used at each hospital. Because of the different assays used, we could only categorize these patients as those with normal or elevated plasma troponin levels, without the possibility of assessing the association between different troponin values and outcomes. Given the logistical limitations during this emerging outbreak, other laboratory data, such as natriuretic peptides, were not collected in all patients. Similarly, echocardiographic data were not collected routinely in most of the patients.

Conclusions

In conclusion, elevated plasma troponin levels were found in up to 45% of patients admitted for COVID-19 in Italian cardiology units. Elevated troponin levels on admission were associated with higher rates of in-hospital complications and in-hospital mortality, and these associations were independent from concomitant cardiac disease and other baseline variables. Diagnostic workup including markers of myocardial injury may be helpful to stratify patients with COVID-19 at hospital admission, so that patients in need of more intensive care may be identified.

ARTICLE INFORMATION

Accepted for Publication: July 3, 2020.

Published Online: August 26, 2020. doi:10.1001/jamacardio.2020.3538

Author Affiliations: Cardiology, ASST Spedali Civili di Brescia, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy (Lombardi, Carubelli, Inciardi, Maccagni, Tomasoni, Metra); Cardiology Unit, Cardiovascular Department, Papa Giovanni XXIII Hospital–Bergamo, Bergamo, Italy (Iorio, Pozzi, Senni); Innovation and Brand Reputation Unit, Papa Giovanni XXIII Hospital, Bergamo, Italy (Bellasi); IRCCS Ospedale Policlinico San Martino–IRCCS Italian Cardiovascular Network, Department of Internal Medicine, University of Genova, Genova, Italy (Canale, Giovinazzo, Ameri, Porto); Intensive Cardiac Care Unit, Fondazione IRCCS Policlinico S. Matteo, Pavia, Italy (Camporotondo, Gnecchi, Leonardi); Cardiology Department, Policlinico di Monza, Monza, Italy (Catagnano, Margonato, Mortara); Istituti Clinici Scientifici Maugeri, IRCCS, Dipartimento di Cardiologia, Istituto Scientifico di Milano, Milan, Italy (Dalla Vecchia); Division of Cardiology, Ospedale di Cremona, Cremona, Italy (Maccagni, Danzi); Centro Cardiologico Monzino, IRCCS, Milan, Italy (Mapelli, Agostoni); Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy (Mapelli, Peveri, Agostoni); Department of Cardiology, University of Pavia, Pavia, Italy (Margonato); Istituto Clinico Casal Palocco, Rome, Italy (Monzo); Policlinico Casilino, Rome, Italy (Monzo); Cardiovascular Department, Azienda Sanitaria Universitaria Giuliano Isontina (ASUGI), and Department of Medical Surgical and Health Sciences, University of Trieste, Trieste, Italy (Nuzzi, Merlo, Sinagra); Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy (Oriecuia, Peveri, Specchia); Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, University of Brescia, Brescia, Italy (Oriecuia); Division of Cardiology, Ospedale San Paolo, ASST Santi Paolo e Carlo, University of Milan, Milan, Italy (Provenzale, Carugo); Cardiovascular Rehabilitation Unit, Buccheri La Ferla Fatebenefratelli Hospital, Palermo, Italy (Sarullo); Department of Molecular Medicine, Cardiology Unit, University of Pavia, Pavia, Italy (Gnecchi, Leonardi); Heart Failure Unit, Cardiology Department, University of Milan, Milan, Italy (Guazzi); IRCCS Policlinico San Donato, Milan, Italy (Guazzi); Istituti Clinici Scientifici Maugeri, IRCCS, Dipartimento di Cardiologia, Istituto Scientifico di Montescano, Pavia, Italy (La Rovere); Heart Failure Unit, Guglielmo da Saliceto Hospital, AUSL Piacenza, Piacenza, Italy (Piepoli); Institute of Life Sciences, Sant'Anna School of Advanced Studies, Pisa, Italy (Piepoli); Department of Cardiovascular and Respiratory Sciences, IRCCS, San Raffaele Pisana Rome, Rome, Italy (Volterrani).

Author Contributions: Drs Metra and Specchia had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Dr Lombardi and Dr Carubelli contributed equally to this work and are co–first authors.
Concept and design: Lombardi, Carubelli, Iorio, Inciardi, Catagnano, Sinagra, Metra, Senni.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Lombardi, Carubelli, Inciardi, Canale, Maccagni, Oriecuia, Peveri, Tomasoni, Carugo, Specchia, Metra, Senni.
Critical revision of the manuscript for important intellectual content: Lombardi, Carubelli, Iorio, Inciardi, Bellasi, Camporotondo, Catagnano, Dalla Vecchia, Giovinazzo, Mapelli, Margonato, Monzo, Nuzzi, Pozzi, Provenzale, Sarullo, Ameri, Gnecchi, Leonardi, Merlo, Agostoni, Danzi, Guazzi, La Rovere, Mortara, Piepoli, Porto, Sinagra, Volterrani, Metra, Senni.
Statistical analysis: Oriecuia, Peveri, Carugo, Specchia, Metra.
Administrative, technical, or material support: Iorio, Bellasi, Maccagni, Margonato, Monzo, Nuzzi, Pozzi, Provenzale, Piepoli.
Supervision: Inciardi, Catagnano, Dalla Vecchia, Ameri, Leonardi, Guazzi, La Rovere, Mortara, Piepoli, Porto, Sinagra, Senni.
Other: Camporotondo.

Conflict of Interest Disclosures: Dr Carubelli received consulting honoraria from CVie Therapeutics Limited, Servier, and Windtree Therapeutics outside the submitted work. Dr Ameri reported having received speaker and advisor honoraria from Novartis, AstraZeneca, Vifor, Daiichi Sankyo, Boehringer Ingelheim, Pfizer, GlaxoSmithKline, and Merck, Sharp & Dohme and nonfinancial support from Actelion outside the submitted work. Dr Leonardi reported grants and personal fees from AstraZeneca and personal fees from BMS/Pfizer, Novo Nordisk, and Chiesi outside the submitted work. Dr Agostoni reported nonfinancial support from Menarini, Novartis, and Boehringer; grants from Daiichi Sankyo and Bayer; and grants and nonfinancial support from Actelion outside the submitted work. Dr Mortara reports personal consulting honoraria from Novartis, Servier, Astra Zeneca for participation to advisory board meetings and receives grants from Novartis and Niccomo for research trials. Dr Piepoli reported having received research grants and speaking fees from Novartis, Servier, and TRX and nonfinancial support from Vifor outside the submitted work. Dr Metra reported personal consulting honoraria from Abbott Vascular, Amgen, Bayer, Edwards Therapeutics, Servier, Vifor Pharma, and Windtree Therapeutics for participation to advisory board meetings and executive committees of clinical trials. Dr Senni reported personal fees from Novartis, Abbott, Merck, Bayer, Boehringer, Vifor, and AstraZeneca outside the submitted work. No other disclosures were reported.

REFERENCES

1. McCarthy CP, Raber I, Chapman AR, et al. Myocardial injury in the era of high-sensitivity cardiac troponin assays: a practical approach for clinicians. *JAMA Cardiol*. 2019;4(10):1034-1042. doi:10.1001/jamacardio.2019.2724

2. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020. doi:10.1001/jamacardio.2020.0950

3. Wei JF, Huang FY, Xiong TY, et al. Acute myocardial injury is common in patients with covid-19 and impairs their prognosis. *Heart*. 2020; heartjnl-2020-317007. doi:10.1136/heartjnl-2020-317007

4. Guo T, Fan Y, Chen M, et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. 2020. doi:10.1001/jamacardio.2020.1017

5. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3

6. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *JAMA*. 2020. doi:10.1001/jama.2020.4683

7. Richardson S, Hirsch JS, Narasimhan M, et al; and the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020. doi:10.1001/jama.2020.6775

8. Inciardi RM, Adamo M, Lupi L, et al. Characteristics and outcomes of patients hospitalized for COVID-19 and cardiac disease in Northern Italy. *Eur Heart J*. 2020;41(19):1821-1829. doi:10.1093/eurheartj/ehaa388

9. Grasselli G, Pesenti A, Cecconi M. Critical care utilization for the COVID-19 outbreak in Lombardy, Italy: early experience and forecast during an emergency response. *JAMA*. 2020. doi:10.1001/jama.2020.4031

10. Lala A, Johnson KW, Januzzi JL, et al; Mount Sinai Covid Informatics Center. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. *J Am Coll Cardiol*. 2020;S0735-1097(20)35552-2. doi:10.1016/j.jacc.2020.06.007

11. Madjid M, Safavi-Naeini P, Solomon SD, Vardeny O. Potential effects of coronaviruses on the cardiovascular system: a review. *JAMA Cardiol*. 2020. doi:10.1001/jamacardio.2020.1286

12. Liu PP, Blet A, Smyth D, Li H. The science underlying COVID-19: implications for the cardiovascular system. *Circulation*. 2020;142(1):68-78. doi:10.1161/CIRCULATIONAHA.120.047549

13. Bonow RO, Fonarow GC, O'Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. *JAMA Cardiol*. 2020. doi:10.1001/jamacardio.2020.1105

14. Tomasoni D, Italia L, Adamo M, et al. COVID-19 and heart failure: from infection to inflammation and angiotensin II stimulation, searching for evidence from a new disease. *Eur J Heart Fail*. 2020. doi:10.1002/ejhf.1871