Evolution of Management and Outcomes of Patients with Myocardial Injury During the COVID-19 Pandemic

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Cardiac involvement in coronavirus disease 2019 (COVID-19) has been established. This is manifested by troponin elevation and associated with worse patient prognosis. We evaluated whether patient outcomes improved as experience accumulated during the pandemic. We analyzed COVID-19-positive patients with myocardial injury (defined as troponin elevation) who presented to the MedStar Health system (11 hospitals in Washington, DC, and Maryland) during the "Early Phase" of the pandemic (March 1 − June 30, 2020) and compared their characteristics and outcomes to the COVID-19-positive patients with the presence of troponin elevation in the "Later Phase" of the pandemic (October 1, 2020 − January 31, 2021). The cohort included 788 COVID-19-positive admitted patients for whom troponin was elevated, 167 during the "Early Phase" and 621 during the "Later Phase." Maximum troponin-I in the "Early Phase" was 13.46±34.72 ng/mL versus 11.21± 20.57 ng/mL in the "Later Phase" (p = 0.553). In-hospital mortality was significantly higher in the "Later Phase" (50.3% vs. 24.6%; p<0.001), as were incidence of intensive-care-unit admission (77.8% vs. 46.1%; p<0.001) and need for mechanical ventilation (61.7% versus 28%; p<0.001). In addition, more "Early Phase" patients underwent coronary angiography (6% vs. 2.3%; p=0.013). Finally, 3% of "Early Phase" and 0.8% of "Later Phase" patients underwent percutaneous coronary intervention (p=0.025). In conclusion, treatment outcomes have significantly improved since the beginning of the pandemic in COVID-19-positive patients with troponin elevation. This may be attributed to awareness, severity of the disease, improvements in therapies, and provider experience. © 2021 Published by Elsevier Inc. (Am J Cardiol 2021;157:42−47)

Patients infected with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in coronavirus disease 2019 (COVID-19), can develop cardiac damage [1,2], with high prevalence in hospitalized patients[3] and poor in-hospital outcomes [4-6]. Furthermore, patients with known cardiovascular disease are at an increased risk of developing the more severe form of COVID-19[7]. In the United States, during the early stages of the pandemic, deferral of elective procedures, including coronary angiography and percutaneous coronary intervention (PCI) for stable coronary disease[8], was recommended to maximize hospital capacity. Management of patients with ST-segment elevation myocardial infarction (STEMI) amid COVID-19 was controversial at first, with some advocating for fibrinolytics to mitigate delays and protect healthcare workers[9]. However, it was soon realized that some of these patients have no culprit vessel on angiography,

and it was found that this treatment strategy increased mortality[10]. Given these concerning findings, guidelines reinforced primary PCI as the standard of care for STEMI and non-ST-elevation myocardial infarction (NSTEMI) in patients with high-risk features[11,12]. As data accumulated early in the pandemic, hospitals quickly adapted and evolved to better treat COVID-19 patients. In the present study, we describe our healthcare system's experience of COVID-19 patients with troponin elevation during the "Early Phase" of the pandemic and see how patient characteristics and outcomes have changed during the "Later Phase" of the pandemic.

Methods

We analyzed COVID-19-positive patients with concomitant troponin elevation (defined as ≥1.0 ng/mL) who presented to the MedStar Health system (11 hospitals in Washington, DC, and Maryland) during the pandemic era. The "Early Phase" of the pandemic was identified as March 1, 2020, through June 30, 2020, and the "Later Phase" of the pandemic was identified as October 1, 2020, through January 31, 2021. These dates were chosen, as they captured the initial wave and third phase of the COVID-19 pandemic in the United States. Of note, our analysis was

performed prior to public rollout of the COVID-19 vaccines. The positive test for the infection was based on polymerase chain reaction testing and the patient having respiratory symptoms and/or chest x-ray or computed tomography findings. Drawing of troponins was not standardized and was at the discretion of the provider. The troponin value recorded was the peak value during the hospitalization. In our analysis, we included cardiac troponin I (cTnI; upper limit of normal, 0.03 ng/mL) or high-sensitivity cardiac troponin (hs-cTnI; upper limit of normal, 30 ng/mL), which are common troponin markers collected in our healthcare system. We identified significant presence of cTnI as an elevation >1 ng/mL or hs-cTnI >30 ng/mL.

Baseline patient characteristics were collected for each cohort. In this analysis, the co-morbidities were identified using International Classification of Diseases, Tenth Revision, codes. Laboratory data, intensive-care-unit (ICU) admission, ICU length of stay, and use of ventilation were compared between the two groups. The primary endpoint was in-hospital mortality. The secondary endpoints include ICU admission, ICU length of stay, use of ventilation, use of coronary angiography, and whether or not PCI was performed. Hospital admission, ICU admission, ventilation, and angiography were not protocolized, and all were under the discretion of the providing team at the respective hospital. The study was conducted in accordance with the Declaration of Helsinki and was approved by our institutional review board.

Descriptive statistics such as frequencies, mean and standard deviation, median and interquartile range were used to describe the study population. Shapiro-Wilk test is used to test the goodness-of-fit of the normal distribution. Student's t-test was used to compare means of Gaussian variables, and Kruskal-Wallis test was used to compare distributions of variables that were otherwise not normally distributed. Chi-squared test was used to compare categorical variables. Odds ratio with respect to in-hospital mortality was estimated from a multivariate logistic regression. Statistical significance was considered to be a p-value <0.05. All analyses were done in SAS 9.4. One author (BCC) has full access to all the data in the study and takes full responsibility for its integrity and the data analysis.

Results

The cohort included 788 COVID-19-positive admitted patients for whom cTnI or hs-cTnI was elevated, 167 during the "Early Phase" and 621 during the "Later Phase." A difference in the total number of patients in the two cohorts may be due to more robust testing in the hospital during the "Later Phase" as compared to the "Early Phase." Baseline characteristics are displayed in Table 1. The majority of patients were men with a mean age of 70.2±14.9 years. Patients treated during the "Early Phase" tended to be slightly younger than those treated during the "Later Phase." Rates of co-morbidities, such as hypertension, hyperlipidemia, diabetes, chronic kidney disease, asthma, chronic obstructive pulmonary disease, coronary artery disease (CAD), congestive heart failure, prior pulmonary embolism, and atrial fibrillation, were similar between the groups. The baseline incidence of stroke and hemodialysis

use was significantly higher in "Early Phase" patients. During hospital admission, white blood cell count, C-reactive protein, lactate dehydrogenase, and ferritin were all significantly lower in the "Later Phase" cohort. Similarly, maximum measured creatinine was statistically higher in the "Early Phase" group than in the "Later Phase" group. Troponin values did not differ significantly between the two groups. Finally, there was a racial disparity in our data: patients in the "Early Phase" were more likely to be Black than those in the "Later Phase", while patients in the "Later Phase" were more likely to be White than those in the "Early Phase." Laboratory data are displayed in Table 2.

In terms of our primary endpoint, in-hospital mortality was significantly higher (50.3%) in "Early Phase" patients than in "Later Phase" patients (24.6%; p <0.001). With regard to our secondary endpoints, the majority of COVID-19-positive patients with troponin elevation from both cohorts were admitted to the ICU, but this was observed significantly more frequently in "Early Phase" patients than in "Later Phase" patients. Similarly, 61.7% of those in the "Early Phase" received mechanical ventilation, as compared to 28% in the "Later Phase" arm (p <0.001) (Figure 1). There were no significant differences in mean length of stay in the ICU between the two groups. Finally, "Early Phase" patients were statistically more likely to undergo coronary angiography than "Later Phase" patients and were similarly more likely to require PCI. Primary and secondary endpoint data are displayed in Table 3. Finally, odds ratio with respect to in-hospital mortality was estimated from a multivariate logistic regression, and results are in Table 4. Early phase, age, and presence of hemodialysis all appeared to be significant.

Discussion

The primary findings of our analysis suggest that in-hospital outcomes (in-hospital mortality, admissions to the ICU, and mechanical ventilation) have improved through the course of the pandemic in COVID-19-positive patients with concomitant troponin elevation. While patients with pre-existing co-morbidities are at increased risk of COVID-19-related adverse outcomes[13,14], the observations in our analysis may be due to changes in treatment strategies, as there was no significant difference in the prevalence of co-morbidities between the two groups. However, this is only hypothesis-generating. In addition, as it is known that patients infected with SARS-CoV-2 have elevated inflammatory markers[15] and that higher levels of these makers are associated with worsening severity of the illness and worse outcomes[16], it is expected that our analysis revealed that sicker patients in the "Early Phase" cohort had significant elevations in all of these markers. This reiterates the importance of checking these markers, as they may help predict outcomes and guide treatment.

One explanation of the favorable outcome in the "Later Phase" can be attributed to disease awareness and early admission of these patients to the hospital for treatment. Early in the pandemic, there were fears of patients going into the hospital due to risk of SARS-CoV-2 infection. Patients might have waited at home in pain longer during the "Early Phase" because they feared contracting the virus

Table 1

Baseline characteristics of COVID-19 patients with troponin elevation overall and "early" versus "later" phase of pandemic

Variable	Overall (n = 788)	Early Phase (n = 167)	Later Phase (n = 621)	p-value
Age (Median, Q1-Q3)	71.3 [61.2 − 81.5]	69.0 [59.7 − 76.8]	72.30 [61.5 − 82.1]	0.018
Male	54.3% (428)	51.5% (86)	55.1% (342)	0.410
White	34.8% (270)	20.0% (33)	38.9% (237)	<0.001
Black	56.0% (434)	67.9% (112)	52.8% (322)	<0.001
Asian	1.3% (10)	0.6% (1)	1.5% (9)	0.380
Native American	0.1% (1)	0.6% (1)	0.0% (0)	0.054
Other	7.7% (60)	10.9% (18)	6.9% (42)	0.086
Hypertension	51.1% (403)	49.1% (82)	51.7% (321)	0.552
Hyperlipidemia	52.9% (417)	58.1% (97)	51.5% (320)	0.132
Diabetes mellitus	48.9% (385)	54.5% (91)	47.3% (294)	0.101
Chronic Kidney Disease	40.6% (320)	44.3% (74)	39.6% (246)	0.272
Hemodialysis	13.8% (109)	19.2% (32)	12.4% (77)	0.025
Chronic Obstructive Pulmonary Disease	15.6% (123)	13.8% (23)	16.1% (100)	0.461
Asthma	5.1% (40)	4.8% (8)	5.2% (32)	0.850
Coronary Artery Disease	32.0% (252)	33.5% (56)	31.6% (196)	0.628
Stroke	12.9% (102)	21.0% (35)	10.8% (67)	<0.001
Congestive Heart Failure	34.5% (272)	36.5% (61)	34.0% (211)	0.538
Atrial Fibrillation	21.4% (169)	19.8% (33)	21.9% (136)	0.550
Prior Pulmonary Embolism	0.1% (1)	0.0% (0)	0.2% (1)	0.604

Q − Quartile

Table 2

Laboratory data of COVID-19-positive patients with troponin elevation overall and "early" versus "later" phase of pandemic

Variable	Overall Median [Q1- Q3] (n = 788)	Early Phase Median [Q1- Q3] (n = 167)	Later Phase Median [Q1- Q3] (n = 621)	p-value*
Maximum Troponin-I (ng/mL)	3.0 [2.0 − 6.0]	2.0 [2.0 − 6.0]	3.0 [2.0 - 8.0]	0.2437
Time to Maximum Troponin-I (hours)	17.8 [4.7 − 67.1]	20.2 [6.1 − 73.3]	12.7 [-0.2 − 23.5]	0.0145
Maximum High-Sensitivity Troponin-I (ng/mL)	104.5 [47.0 − 375.0]	76.0 [49.0 − 917.0]	77.0 [44.0 = 238.0]	0.7563
Time to Maximum High-Sensitivity Troponin -I (hours)	2.4 [-2.6 − 18.7]	87.6 [1.6 − 168.2]	2.3 [-.2.7 − 18.5]	0.0543
N-terminal-pro-hormone BNP (ng/L)	3038 [599 − 16014.0]	3252.5 [593.0 − 15173.0]	2889.5 [770.0 − 20821.0]	0.6995
Maximum Creatinine (mg/dL)	2.0 [1.0 − 4.0]	3.0 [2.0 − 6.0]	2.0 [1.0 − 4.0]	<0.001
Maximum White Blood Cell (K/μL)	9.0 [8.0 − 10.0]	10.0 [9.0 − 10.0]	9.0 [8.0 − 10.0]	0.001
C-Reactive Protein (mg/dL)	79.0 [42.0 − 105.5]	97.5 [64.0 − 190.0]	76.0 [38.0 − 97.0]	<0.001
Lactate Dehydrogenase (U/L)	477.5 [342.5 − 656.5]	616.0 [482.0 − 804.0]	426.0 [324.0 − 581.0]	<0.001
Ferritin (ng/mL)	807.5 [386.0 − 1601.0]	919.0 [631.0 − 3461.0]	754.0 [344.0 − 1345.0]	<0.001

*Kruskal Wallis p-value

in the emergency room and because of lockdown uncertainty, resulting in a more severe presentation and worse outcomes[17]. Furthermore, throughout the course of the COVID-19 pandemic, treatment strategies have evolved significantly as guidelines have changed and clinical knowledge has improved. In the early stages of the pandemic, the standard of care was initially supportive, including the use of supplemental oxygen, prone positioning[18,19], conservative fluid management[20], prophylactic antibiotics, management of co-morbidities, and avoiding mechanical ventilation whenever possible. More recently, the use of colchicine and, more importantly, corticosteroids, in particular dexamethasone, is recommended in COVID-19 patients who require supplemental oxygen to decrease all-cause mortality[21]. Other treatment strategies include convalescent plasma infusions[22]. Finally, in October 2020, the antiviral medication remdesivir received emergency use authorization from the US Food and Drug Administration, as the medication reduced time to recovery in those

hospitalized with COVID-19[23]. However, more recent data on remdesivir may not support this finding as strongly[24].

Our analysis revealed that patients in the "Early Phase" were more likely to undergo both coronary angiography and PCI. We hypothesize that this reflects a change in understanding in the role of troponins in COVID-19 infection. Early in the pandemic, providers might have been more likely to regard elevated troponins as a marker of obstructive CAD and recommend angiography. Later in the pandemic, providers might have been aware of the increasing evidence that troponin elevations are seen in COVID-19 patients without obstructive CAD and, thus, chose to forgo invasive testing. Particular attention has been directed toward the management of acute coronary syndrome during the COVID-19 pandemic. In patients with STEMI or NSTEMI with high-risk features, in which the etiology of their acute myocardial infarction is suspected to be true plaque rupture and not myocarditis or stress-induced cardiomyopathy in the setting of COVID-19 infection, our

In-Hospital Outcomes COVID-19 Patients with Troponin Elevation During Pandemic

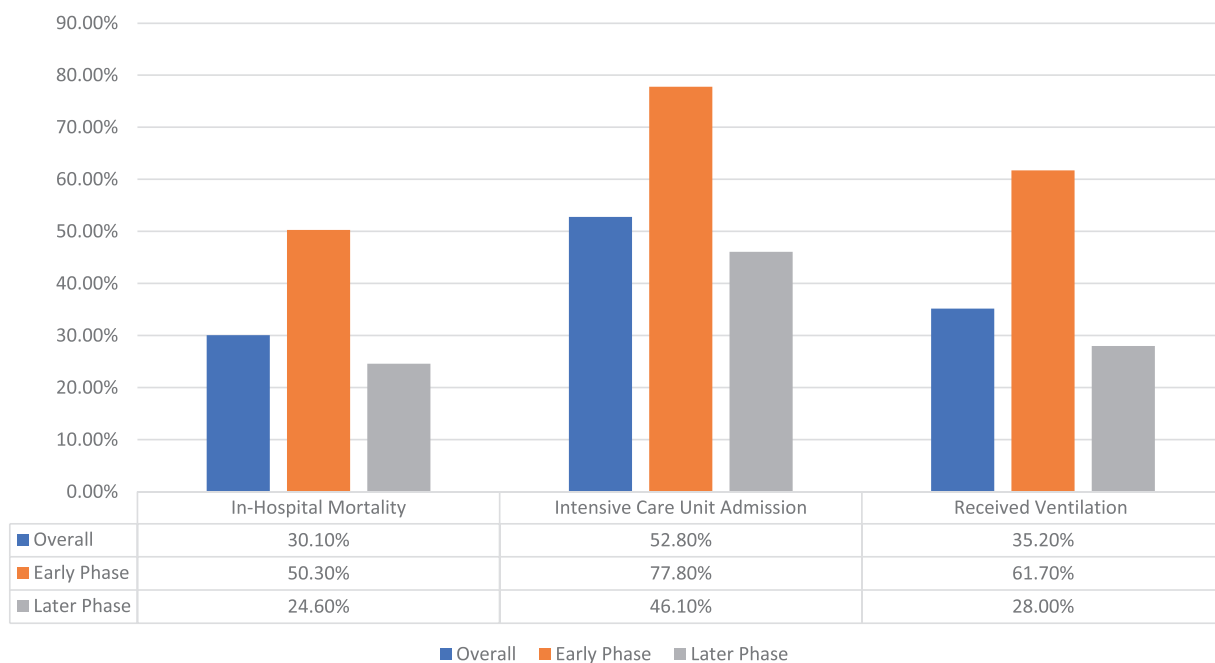|	In-Hospital Mortality	Intensive Care Unit Admission	Received Ventilation
Overall	30.10%	52.80%	35.20%
Early Phase	50.30%	77.80%	61.70%
Later Phase	24.60%	46.10%	28.00%

Figure 1. Overall in-hospital outcomes in COVID-19 patients with troponin elevation during the pandemic

Table 3

Primary and secondary outcomes: Laboratory values, intensive care unit, and cardiac catheterization data of COVID-19-positive patients overall and "early" versus "later" phase of pandemic

Variable	Overall (n = 788)	Early Phase (n = 167)	Later Phase (n = 621)	p-value
Overall In-Hospital Mortality	30.1% (236)	50.3% (84)	24.6% (152)	<0.001
Intensive Care Unit Admission	52.8% (416)	77.8% (130)	46.1% (286)	<0.001
Received Ventilation	35.2% (277)	61.7% (103)	28.0% (174)	<0.001
Length of Stay in Intensive Care Unit (Days)*	6.22 [2.5 − 12.5]	5.3 [2.4 − 12.2]	6.8 [2.6 − 12.7]	0.434
Coronary Angiography	3.0% (24)	6.0% (10)	2.3% (14)	0.013
Percutaneous Coronary Intervention	1.3% (10)	3.0% (5)	0.8% (5)	0.025

*Median [Quartile 1 − Quartile 3]

cardiac catheterization laboratory implemented procedures to ensure safety of medical personnel during primary PCI. Per guidelines[12], we trained everyone in the catheterization lab on proper personal-protective-equipment use, designated one laboratory for COVID-19-positive patients or those under investigation, and performed extensive cleaning after each procedure. We also implemented new

Table 4

Adjusted In-Hospital Mortality in COVID-19 Patients. Adjusted odds ratios of early vs later outcomes, adjusting for relevant baseline differences

Variable	Odds Ratio	95% Confidence Interval
Early Phase	3.04	2.08 − 4.44
Age	1.022	1.01 − 1.03
White Race	1.00	0.7 − 1.44
Hemodialysis	0.25	0.12 − 0.49
Stroke	1.36	0.86 − 2.17
Creatinine	1.19	1.11 - 1.29

treatment and risk-stratification algorithms, utilizing non-invasive diagnostic testing such as echocardiogram and cardiac magnetic resonance imaging in patients with low-risk features, ensuring that only high-risk COVID-19 patients with suspected plaque rupture were brought to the catheterization laboratory[25]. Non-invasive imaging allows for the diagnosis of disease processes such as stress-induced cardiomyopathy or pericarditis, which is prevalent in COVID-19 patients, and these patients can avoid going to the catheterization laboratory.

There are limitations to our study. First, the analysis is retrospective and relies on International Classification of Diseases, Tenth Revision, codes to identify the patient population. As inclusion in our analysis depended only on a positive COVID-19 test and a positive troponin, it did not distinguish between Type I and Type II NSTEMI, nor did it analyze whether patients had electrocardiographic changes and/or symptoms consistent with myocardial ischemia. In addition, the drawing of troponin in COVID-19 patients

was not standardized and was under the discretion of the provider. Further, while guidelines did not initially recommend drawing troponin in the absence of chest pain, some sources now recommend that providers obtain troponin in addition to other inflammatory markers. This may explain why the "Later Phase" cohort contains more patients than the "Early Phase" cohort. Further, while we captured whether patients underwent coronary angiography and subsequent PCI, we did not capture the indication for the procedure nor the reasons that some patients had coronary angiography but not PCI. Further analysis of these data would have allowed us to more completely separate those with obstructive CAD from those with other etiologies of myocardial injury (e.g., myocarditis or stress-induced cardiomyopathy)[26]. We also did not capture how patients were treated (pharmacology, mechanical support, etc.). As such, although we believe that treatment methodologies differed between our two cohorts based on the date of their hospitalization, we cannot be certain. Finally, our data captured patients in the Mid-Atlantic region of the US, where the pandemic was most impactful in March and April 2020. Our findings may not represent the broader US outcome data.

In conclusion, COVID-19-positive patients with elevated troponin during the "Later Phase" of the pandemic tended to have improved outcomes, including improved in-hospital mortality, fewer ICU admissions, and less use of mechanical ventilation. They were also less likely to undergo invasive cardiac testing. Despite a similar baseline incidence of many co-morbidities, those in the "Later Phase" had decreased inflammatory markers and were less likely to have an acute kidney injury during their hospitalization. This improvement in outcomes probably reflects advances in available COVID-19 treatment options, as well as provider experience with the novel disease.

Disclosure

Toby Rogers − Proctor and Consultant: Medtronic, Edwards Lifesciences; Advisory Board: Medtronic; Equity interest: Transmural Systems.

William S. Weintraub − Research support: Amarin Corporation, National Institutes of Health; Consultant: Amarin Corporation, AstraZeneca, Janssen, SC Pharma, The Medicines Company.

Ron Waksman − Advisory Board: Abbott Vascular, Amgen, Boston Scientific, Cardioset,

Cardiovascular Systems Inc., Medtronic, Philips, Pi-Cardia Ltd.; Consultant: Abbott Vascular, Amgen, Biotronik, Boston Scientific, Cardioset, Cardiovascular Systems Inc.,

Medtronic, Philips, Pi-Cardia Ltd., Transmural Systems; Grant Support: AstraZeneca, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance; Transmural Systems.The authors declare the following financial interests/personal relationships which may be considered as potential

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