



The Role of Cardiac Biomarkers as Predictors of In-hospital Mortality among COVID patients in a Tertiary Hospital in Metro Manila, Philippines

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ABSTRACT

BACKGROUND

Coronavirus disease 2019 (COVID-19) has been declared a global pandemic. The overwhelming volume of confirmed cases makes prevention and control a challenge. Despite this, numerous knowledge gaps remain in the diagnosis, management and prognostication of this novel coronavirus infection.

METHODS

This retrospective cohort study included patients with polymerase chain reaction confirmed COVID-19. Binary logistic regression was used to determine the association between the cardiac biomarkers and in-hospital mortality. ROC, AUC and cutoff analyses were used to determine optimal cutoff values for the cardiac biomarkers.

RESULTS

Out of 224 rRT-PCR confirmed cases, 90 subjects with a complete panel of cardiac biomarkers were included in this study. Sixty-six (77.6%) subjects survived, five were still admitted while 19 (22.4%) expired. Logistic regression analysis showed that creatine kinase and hsTnI were independently associated with in-hospital mortality (OR, 4.103 [95% CI, 1.241-13.563], $p = 0.021$; and OR, 7.899 [95% CI, 2.430-25.675], $p = 0.001$, respectively). ROC curve analysis showed that hsTnI was a good predictor for in-hospital mortality (AUC, 0.829 [95% CI, 0.735-0.923], $p = <0.001$). Optimal cutoff point derived from the ROC curve for hsTnI was 0.010 ng/ml (J, 0.574) with a sensitivity of 84% (TPR, 0.842 [95%CI, 0.604-0.966]), specificity of 73% (TNR, 0.732 [95% CI, 0.614-0.886]), an adjusted negative predictive value of 99% (Known prevalence*adjusted NPV, 0.989), a positive likelihood ratio of 20% (LR+, 3.147 [95% CI, 2.044-4.844]).

CONCLUSION

High sensitivity troponin I level was a good tool in significantly predicting in-hospital mortality.

INTRODUCTION

After coronavirus disease 2019 (COVID-19) has been declared a pandemic, there are now 6,702,699 COVID-19 cases worldwide, with a computed prevalence rate of 83.8 per 100,000 and incidence rate of 38.2 per 100,000.¹ As of May 2020, the Philippines ranks 39th out of the 215 countries in the number of cases with a case fatality rate of 4.4%. As the viral pandemic decimates lives and paralyzes economies, numerous knowledge gaps remain in the diagnosis, management and prognostication of this novel coronavirus infection.

This study aimed to determine the role of cardiac biomarkers as predictor of in-hospital mortality among nucleic acid amplification test (*real-time* reverse transcriptase polymerase chain reaction or RT-PCR) positive patients for SARS-CoV-19 in Makati Medical Center (MMC), a 600-bed capacity tertiary facility in Makati City, Metro Manila, Philippines which was one of the frontline institutions in the National Capital Region of the Philippines which battled the first wave of COVID-19 starting in March 2020.

METHODS

This was a retrospective cohort of consecutive rRT-PCR seropositive COVID-19 patients, aged 18-90 years, admitted at MMC from February 1 to April 30, 2020. Those who stayed in the hospital for less than six hours and those with no determination of cardiac biomarkers were excluded. The patients were grouped into non-severe and severe categories (the severe and critical cases were grouped all together). Further, each category was subcategorized as to the final clinical outcome – survivors and non-survivors.

All data were extracted from electronic medical records and patient charts: demographic data, i.e., age, sex, occupation, body mass index, exposure and smoking history; clinical data, i.e., signs or symptoms upon presentation, oxygen saturations, and supplementations given, pre-existing comorbidities, complications, and clinical outcome.

The results of the following laboratory parameters were noted at baseline contact: complete blood count, platelet count, creatinine, sodium, potassium, aspartate aminotransaminase (AST), alanine aminotransferase (ALT), ferritin, C-reactive protein (CRP), procalcitonin, lactate dehydrogenase (LDH), hs troponin I (hsTnI), total creatine kinase (tCK) and creatine kinase-MB (CK-MB) isoenzyme. Data were entered into a password-protected computerized database, cross-checked and encrypted.

The diagnosis was based on the World Health Organization (WHO) interim guidelines.² A confirmed case of COVID-19 was defined as a positive result on the rRT-PCR assay of nasopharyngeal and oropharyngeal swab specimens. Non-severe cases are patients with uncomplicated upper respiratory tract infection with non-specific symptoms such as fever, fatigue, cough (with or without sputum production), respiratory rate of fewer than 30 breaths/min, and sPO₂ more than 93% at room air; severe cases are patients with severe pneumonia with either one of the following: dyspnea, the respiratory rate more than 30 breaths/min, sPO₂ less than or equal to 93% at room air, the partial pressure of arterial oxygen to fraction of inspired

oxygen (P/F) ratio of less than 300, sepsis or septic shock, and lung infiltrates more than 50% within 24 to 48 hours; and critical cases are those who are in respiratory failure, necessitating the need for mechanical intubation, septic shock, and/or multiorgan dysfunction or failure.^{3,4} The primary composite end-point was defined as an event where patients required either intensive care monitoring, mechanical intubation and/or death.

The following in-hospital cardiovascular and other complications were defined as follows: acute heart failure syndrome was defined as a change in heart failure signs and symptoms requiring urgent therapy; significant arrhythmia pertained to any of the following, i.e., ventricular tachycardia, atrial/ventricular fibrillation, and ectopic atrial rhythm; vasopressor requiring shock defined as a hemodynamic instability requiring inotropic use; acute respiratory distress syndrome was defined according to the Berlin definition of 2012;⁵ acute kidney injury was defined according to the Kidney Disease Improving Global Outcomes guidelines.⁶

This study was conducted in compliance with all local and national regulations and guidelines and in accordance with the International Conference on Harmonization and Good Clinical Practice. The protocol of this study was reviewed and approved by the MMC Institutional Review Board. The privacy and confidentiality of data were maintained in compliance with the Philippine Data Privacy Act of 2012. The authors had no conflicts of interest in the study.

STATISTICAL ANALYSIS

Categorical variables were shown as counts and percentages, and continuous variables as medians and interquartile ranges (IQR). Mann-Whitney *U* test was performed for continuous variables, and the χ^2 test and Fisher exact test were used for categorical variables as appropriate. The Spearman rho for nonparametric measures was used to measure the degree of association of the cardiac biomarkers with the primary composite endpoint and the disease severity. Kruskal-Wallis H test was used to compare across groups. No imputation was made for missing data.

Binary logistic regression analysis was used to determine the association of cardiac biomarkers with mortality. The odds ratio (OR) along with the 95% confidence interval (CI) were reported. A *p* value of less than 0.05 was regarded as statistically significant. All statistical analyses were performed using IBM SPSS Statistics 22 for Windows, and NCSS 2020 Statistical Software (2020). NCSS, LLC.

RESULTS

After carefully reviewing 224 records of confirmed COVID-19 patients for completion of data, 90 patients with cardiac biomarker determinations were included in this study. In the non-severe category, there were 60 cases, 59 (98.3%) survived and one (1.7%) died; while in the severe category, there were 30 cases of which there were 12 (40%) survivors and 18 (60%) non-survivors.

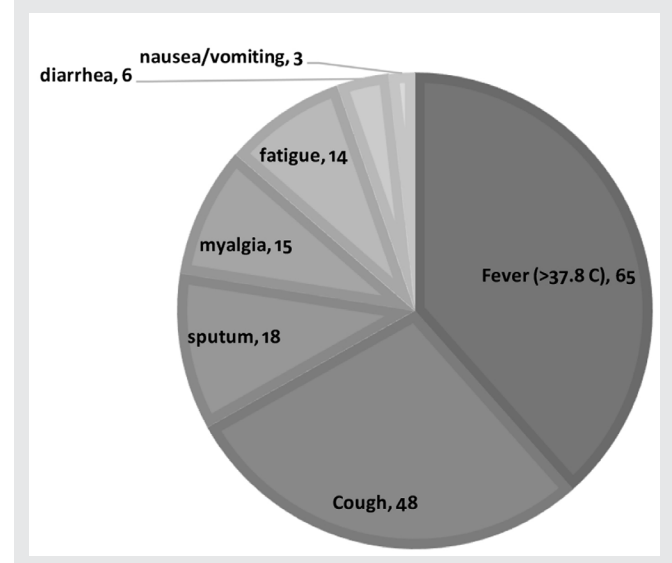
The median age for all patients was 57 years (IQR, 47-67 years). Around seven (40%) of the non-survivors in the severe category were aged 50-59 years, while two (11%) were aged above 80 years. There were significantly more older individuals who died than those who survived. Majority of the patients, 62 (68.9%) were

males, 39 (62.9%) in the non-severe, and 23 (37.1%) in the severe category. A few, 7 (7.8%) were healthcare workers (Table 1).

CLINICAL PROFILE UPON PRESENTATION AND PRE-EXISTING CO-MORBID CONDITIONS

The three most common presenting symptoms were fever (65, 75.6%), cough (48, 55.8%) and sputum production (18, 20.9%) as shown in Figure 1. All patients in the non-severe group (100%; *p* = 0.013) and more than 90% of the non-survivors in the severe group had cough (*p* = 0.003).

Figure 1: Distribution of Symptoms Presented by Patients at the Emergency Department.



The three most common co-morbid conditions were hypertension (61, 67.8%), diabetes mellitus (30, 33.3%) and bronchial asthma (15, 16.7%) as shown in Table 2. Fourteen (15.6%) had chronic cardiac disease, and ten (11.1%) had chronic kidney disease.

LABORATORY FINDINGS

As shown in Table 3, the median lymphocyte count of the non-survivors in the severe category was significantly lower than those who survived (1,250 cells/mm³ [IQR, 850-1,775] vs. 2,000 cells/mm³ [IQR, 1,600-2,700], *p* = 0.001). No statistically significant difference for white blood cell count, platelet count and hemoglobin level in both categories was found.

The median lactate dehydrogenase levels of the survivors, 272.8 U/liter and 323.0 U/liter, were significantly lower than those of the non-survivors, 640.91 U/liter and 391.3 U/liter [IQR, 345.3-514.4], for both the non-severe and the severe groups (*p* < 0.001, and *p* < 0.001, respectively).

In the severe category, the median C-reactive protein levels was significantly higher among the non-survivors (13.9 mg/liter [IQR, 11.5-19.43] vs. 9.84 mg/liter [IQR, 4.88-16.25], *p* < 0.001). Also, the median ferritin levels among those who survived was significantly lower relative to those who did not (1,646.3 μ/liter [IQR, 926.2-2,446.7] vs. 1,859.2 μ/liter [IQR, 1,246-2,671.5], *p* = 0.0010).

The procalcitonin levels was significantly higher among the non-survivors relative to those who survived across both severe (0.60

Table 1. Demographic and Clinical Characteristics of Patients in this Study. *

Parameter	All Patients	Non-severe Category (n = 60)		p value†	Severe Category (n = 30)		p value†
		Survivor (n = 59)	Non-survivor (n = 1)		Survivor (n = 12)	Non-survivor (n = 18)	
Age				0.007			0.015
Median (IQR) – yr	57 (47-67)	54 (45-63)	55 (-)		66 (56-69)	66 (56-76)	
Distribution – no./total no. (%)							
< 20 yr	1/90 (1.1)	1/59 (1.7)	-		-	-	
20 – 29 yr	3/90 (3.3)	3/59 (5.1)	-		-	-	
30 – 39 yr	5/90 (5.6)	5/59 (8.5)	-		1/12 (8.3)	-	
40 – 49 yr	17/90 (18.9)	14/59 (23.7)	-		1/12 (8.3)	2/18 (11.1)	
50 – 59 yr	22/90 (24.4)	15/59 (25.4)	1/1 (100)		2/12 (16.7)	4/18 (22.2)	
60 – 69 yr	28/90 (31.1)	16/59 (27.1)	-		4/12 (33.3)	7/18 (38.9)	
70 – 79 yr	10/90 (11.1)	4/59 (6.8)	-		4/12 (33.3)	3/18 (16.7)	
> 80 yr	3/90 (3.3)	1/59 (1.7)	-		-	2/18 (11.1)	
Sex				0.207			0.289
Distribution – no./total no. (%)							
Male	62/90 (68.9)	38/59 (64.4)	1/1 (100)		9/12 (75.0)	14/18 (77.8)	
Female	28/90 (31.1)	21/59 (35.6)	-		3/12 (25.0)	4/18 (22.2)	
Occupation				0.443			0.647
Distribution – no./total no. (%)							
Healthcare worker	7/90 (7.8)	4/59 (6.8)	-		2/12 (16.7)	1/18 (5.6)	
Non-healthcare worker	83/90 (92.2)	55/59 (93.2)	1/1 (100)		10/12 (83.3)	17/18 (94.4)	
Anthropometrics							
Height				0.370			0.781
Median (IQR) – cm	163.5 (160.0-169.8)	163.0 (157.5-169.0)	173 (-)		169.0 (161.0-170.5)	163.0 (161.5-167.2)	
Standard deviation/Standardization	8.3/-10.3	9.1/-12.5	-		7.3/-21.2	6.3/-23.3	
Weight				0.103			0.140
Median (IQR) – kg	70.0 (60.8-80.9)	66.8 (59.2-80.4)	79.3 (-)		70.0 (67.8-78.0)	70.0 (67.0-90.0)	
Standard deviation/Standardization	16.0/0.5	9.1/-12.5	-		7.3/-21.2	6.3/-23.3	
Body mass index				0.172			0.247
Median (IQR) – kg/m ²	26.3 (24.2-28.5)	25.1 (23.3-28.0)	26.5 (-)		26.0 (24.9-27.4)	27.2 (25.3-29.5)	
Distribution – no./total no. (%)							
Underweight	-	-	-		-	-	
Normal	30/90 (33.3)	24/59 (40.7)	-		3/12 (25.0)	3/18 (16.7)	
Overweight	35/90 (38.9)	18/59 (30.5)	1/1 (100)		7/12 (58.3)	9/18 (50.0)	
Obese class I	11/90 (12.2)	6/59 (10.2)	-		2/12 (16.7)	3/18 (16.7)	
Obese class II	2/90 (2.2)	1/59 (1.7)	-		-	1/18 (5.6)	
Obese class III	1/90 (1.1)	1/59 (1.7)	-		-	-	
Smoking				-			0.766
Median (IQR) – pack years	2.5 (1.0-18.0)	1.5 (1.0-4.8)	-		10.5 (0.8-22.5)	20.0 (16.5/40)	
Distribution – no./total no. (%)							
< 10 pack years	10/90 (11.1)	8/59 (13.6)	-		2/12 (16.7)	-	
10 – 20 pack years	4/90 (4.4)	1/59 (1.7)	-		1/12 (8.3)	2/18 (11.1)	
> 20 pack years	4/90 (4.4)	2/59 (3.4)	-		1/12 (8.3)	1/18 (5.6)	
Exposure				0.453			0.969
Distribution – no./total no. (%)							
With exposure	24/90 (26.7)	15/59 (25.4)	-		4/12 (33.3)	5/18 (27.8)	
Without exposure	44/90 (48.9)	32/59 (54.2)	1/1 (100)		4/12 (33.3)	7/18 (38.9)	

* The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding. IQR denotes interquartile range.

† Level of significance set at *P* value less than 0.05.

‡ Data for fever on admission and symptom presentation are missing in 4.4% of cases.

Table 2. Clinical Profile on Presentation and Pre-existing Co-morbid Conditions of Patients in this Study.*

Parameter	All Patients	Non-severe Category (n = 60)		p value	Severe Category (n = 30)		p value
		Survivor (n = 59)	Non-survivor (n = 1)		Survivor (n = 12)	Non-survivor (n = 18)	
Temperature at the Emergency Room							
Median (IQR) – °C	37.1 (36.5-37.8)	37.0 (36.5-37.8)	37.3 (-)		37.5 (37.0-37.8)	37.7 (37.0-37.9)	
Distribution – no./total no. (%)							
< 37.5 °C	54/86 (62.8)	41/59 (69.5)	1/1 (100)		5/10 (50.0)	7/16 (43.8)	
37.5 – 38.0 °C	17/86 (19.8)	8/59 (13.6)	-		4/10 (40.0)	6/16 (37.5)	
38.1 – 39.0 °C	10/86 (11.6)	7/59 (11.9)	-		1/10 (10.0)	2/16 (12.5)	
> 39 °C	5/86 (5.8)	3/59 (5.1)	-		1/10 (10.0)	1/16 (6.3)	
Fever	65/86 (75.6)	47/59 (79.7)	-	0.022	6/10 (60.0)	11/16 (68.8)	0.245
Cough	48/86 (55.8)	59/59 (100.0)	-	0.013	6/10 (60.0)	15/16 (93.8)	0.003
Sputum production	18/86 (20.9)	13/59 (22.0)	-	0.906	-	5/16 (31.3)	0.441
Myalgia	15/86 (17.4)	8/59 (13.6)	1/1 (100)	0.203	2/10 (20.0)	5/16 (31.3)	0.206
Fatigue	14/86 (16.3)	10/59 (16.9)	-	0.257	2/10 (20.0)	1/16 (6.3)	0.498
Diarrhea	6/86 (7.0)	1/59 (1.7)	-	0.183	2/10 (20.0)	3/16 (18.8)	0.074
Nausea/vomiting	3/86 (3.0)	1/59 (1.7)	-	0.113	-	2/16 (12.5)	0.051
Co-existing disorders							
Distribution – no./total no. (%)							
Diabetes mellitus	30/90 (33.3)	16/59 (27.1)	-	0.131	7/12 (58.3)	7/18 (38.9)	0.716
Hypertension	61/90 (67.8)	36/59 (61.0)	1/1 (100)	0.258	8/12 (66.7)	16/18 (88.9)	0.055
Chronic cardiac disease	14/90 (15.6)	6/59 (10.2)	-	0.138	4/12 (33.3)	4/18 (22.2)	0.459
Cerebrovascular disease	3/90 (3.3)	1/59 (1.7)	-	-	1/12 (8.3)	1/18 (5.6)	0.600
Chronic renal disease	10/90 (11.1)	4/59 (6.8)	-	0.240	2/12 (16.7)	4/18 (22.2)	0.123
Chronic liver disease	2/90 (2.2)	1/59 (1.7)	-	0.391	-	1/18 (5.6)	0.462
Malignancy†	2/90 (2.2)	1/59 (1.7)	-	0.391	-	-	-
Hematologic disease	1/90 (1.1)	1/59 (1.7)	-	0.546	-	-	-
Chronic respiratory disease‡	2/90 (2.2)	-	-	-	1/12 (8.3)	1/18 (5.6)	0.314
Bronchial asthma	15/90 (16.7)	10/59 (16.9)	-	0.525	2/12 (16.7)	3/18 (16.7)	0.909
Thyroid pathology	2/90 (2.2)	2/59 (3.4)	-	0.324	-	-	-
Dyslipidemia	6/90 (6.7)	5/59 (8.5)	-	0.569	-	1/18 (5.6)	-
Any†	20/90 (22.2)	20/59 (33.9)	-	0.577	-	6/18 (33.3)	0.268

* The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding. IQR denotes interquartile range. P value less than 0.05 is considered significant.

† Data for fever on admission and symptom presentation are missing in 4.4% of cases.

‡ Included in this category is any type of cancer.

§ Chronic respiratory disease encompasses physician-diagnosed chronic obstructive pulmonary disease, bronchiectasis, etc.

¶ Other conditions not belonging to the major categories listed, includes: osteoporosis, hyperuricemia, gouty arthritis, impaired fasting glucose, gastroesophageal reflux disease, irritable bowel syndrome, osteoarthritis, and benign prostatic hyperplasia

** The primary composite end point was admission to an intensive care unit, the use of mechanical ventilation, or death.

†† Data for disposition were missing in 5.5% of cases.

Table 3. Ancillary Diagnostics of Patients in this Study.*

Parameter	All Patients	Non-severe Category (n = 60)		p value†	Severe Category (n = 30)		p value†
		Survivor (n = 59)	Non-survivor (n = 1)		Survivor (n = 12)	Non-survivor (n = 18)	
White blood cell count				0.499			0.583
Median (IQR) – 10 ³ /μL	6,300 (5,200-8,800)	6,100 (4,800-8,000)	4,800 (-)		6,700 (5,350-7,600)	18,000 (6,000-12,275)	
Lymphocyte count				0.002			0.001
Median (IQR) – per mm ³	1,900 (1,300-2,600)	2,100 (1,600-2,800)	2,200 (-)		2,000 (1,600-2,700)	1,250 (850-1,775)	
Platelet count				0.156			0.172
Median (IQR) – per mm ³	222,000 (168,000-290,000)	246,000 (173,000-297,000)	144,000 (-)		208,000 (170,000-231,000)	191,000 (158,250-268,750)	
Hemoglobin				0.290			0.229
Median (IQR) - g/dl	14.3 (13.3-15.2)	14.5 (13.1-15.3)	15.3 (-)		14.6 (13.6-14.9)	13.5 (12.3-14.8)	
Lactate dehydrogenase				<0.001			<0.001
Median (IQR) - U/liter	299.3 (244.4-388.2)	272.8 (231-347.4)	640.91 (-)		323.0 (238-376.5)	391.3 (345.3-514.4)	
C-reactive protein				<0.001			<0.001
Median (IQR) - mg/liter	6.1 (1.8-13.8)	4.81 (0.98-6.50)	4.15 (-)		9.84 (4.88-16.25)	13.9 (11.5-19.43)	
Ferritin				<0.001			0.001
Median (IQR) - μl/liter	989.4 (516.6-2,050.4)	710.7 (316.2-1,379.3)	4,805.0 (-)		1,646.3 (926.2-2,446.7)	1,859.2 (1,246-2,671.5)	
Procalcitonin				<0.001			<0.001
Median (IQR) - ng/ml	0.09 (0.04-0.25)	0.05 (0.02-0.12)	0.25 (-)		0.12 (0.06-0.19)	0.60 (0.19-2.01)	
D-dimer				0.054			0.326
Median (IQR) - ng/ml	500 (315-1,076)	395 (261.8-787.5)	-		460 (390.0-2,356.5)	3,535 (1,280-8,326.3)	
Sodium				0.085			0.121
Median (IQR) - mmol/liter	134.5 (131.8-138.1)	134.9 (132.3-138.8)	131.0 (-)		134.0 (132.0-135.3)	133.2 (130.3-137.4)	
Potassium				0.698			0.882
Median (IQR) - mmol/liter	3.8 (3.4-4.2)	3.70 (3.40-4.01)	3.00 (-)		3.96 (3.30-4.30)	3.85 (3.45-4.34)	
Creatinine				0.134			0.067
Median (IQR) - mg/dl	1.0 (0.8-1.2)	0.90 (0.75-1.09)	0.91 (-)		1.06 (0.80-1.21)	1.06 (0.87-1.43)	
Alanine aminotransferase				0.788			0.580
Median (IQR) - U/liter	47.0 (29.9-73.7)	48.96 (29.68-73.75)	50.73 (-)		36.49 (31.64-56.81)	45.20 (38.05-76.41)	
Aspartate aminotransferase				0.012			0.027
Median (IQR) - U/liter	51.2 (40.2-75.3)	48.31 (37.20-61.80)	74.73 (-)		57.49 (46.06-70.59)	55.33 (49.24-81.78)	

* The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding. IQR denotes interquartile range.

† P value less than 0.05 is considered significant.

‡ Data for disposition were missing in 5.5% of cases.

Table 4. Cardiac Biomarkers.*

Parameter	All Patients	Non-severe Category (n = 60)		p value†	Severe Category (n = 30)		p value†
		Survivor (n = 59)	Non-survivor (n = 1)		Survivor (n = 12)	Non-survivor (n = 18)	
Creatine kinase				0.039			0.016
Median (IQR) - U/liter	173.6 (83.4-287.3)	123.98 (76.0-213.1)	463.59 (-)		158.7 (115.0-193.0)	178.7 (149.4-276.6)	
Distribution – no./total no. (%)							
> 168 U/liter	31/60 (51.7)	15/36 (41.7)	1/1 (100)		4/9 (44.44)	11/14 (78.6)	
Median (IQR) - U/liter	170.9 (195.2-419.3)	365.68 (210.7-754.2)	463.59 (-)		195.20 (187.5-217.6)	248.38 (178.7-330.5)	
Creatine kinase-MB isoenzyme				0.079			0.053
Median (IQR) - U/liter	0.6 (0.4-1.3)	0.45 (0.30-0.80)	21.34 (-)		0.50 (0.35-0.85)	1.0 (0.80-1.80)	
Distribution – no./total no. (%)							
> 25 U/liter	4/63 (6.3)	3/38 (7.9)	-		-	1/13 (7.7)	
Median (IQR) - U/liter	274.2 (123.3-431.5)	319.04 (229.2-408.9)	-		-	74.96 (-)	
High sensitivity cardiac troponin I				<0.001			<0.001
Median (IQR) - ng/ml	0.009 (0.004-0.026)	0.006 (0.003-0.01)	0.046 (-)		0.012 (0.005-0.025)	0.028 (0.013-0.127)	
Distribution – no./total no. (%)							
> 0.015 ng/ml	27/80 (33.8)	9/49 (18.4)	1/1 (100)		5/12 (41.7)	12/18 (66.7)	
Median (IQR) - U/liter	0.043 (0.027-0.185)	0.043 (0.024-0.105)	0.046 (-)		0.035 (0.033-0.037)	0.066 (0.029-0.393)	

* The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding. IQR denotes interquartile range.

† P value less than 0.05 is considered significant.

‡ Data for disposition were missing in 5.5% of cases.

Table 5. Complications and Clinical Outcome of Patients in this Study.*

Parameter	All Patients	Non-severe Category (n = 60)		p value†	Severe Category (n = 30)		p value†
		Survivor (n = 59)	Non-survivor (n = 1)		Survivor (n = 12)	Non-survivor (n = 18)	
Cardiovascular complications – no./total no. (%)							
New onset or worsening heart failure	1/90 (1.1)	1/59 (1.7)	-	-	-	-	-
Significant arrhythmia	6/90 (6.7)	-	-	-	3/12 (25.0)	3/18 (16.7)	0.293
Type of arrhythmia							
Ventricular tachycardia	2/90 (2.2)	-	-	-	-	2/18 (11.1)	<0.001
Atrial fibrillation	4/90 (4.4)	-	-	-	3/12 (25.0)	1/18 (5.6)	0.125
Ectopic atrial rhythm	1/90 (1.1)	-	-	-	1/12 (8.3)	-	-
Vasopressor requiring/shock	26/90 (28.9)	2/59 (3.3)	1/1 (100)	0.002	6/12 (50.0)	15/18 (83.3)	0.011
Venous thromboembolism	2/90 (2.2)	-	-	-	1/12 (8.3)	1/18 (5.6)	0.605
Other complications – no./total no. (%)							
Acute respiratory distress syndrome	36/90 (46.8)	8/59 (16.3)	1/1 (100)	<0.001	11/12 (91.7)	16/18 (88.9)	<0.001
Acute kidney injury	23/90 (25.6)	8/59 (13.6)	1/1 (100)	0.001	4/12 (33.3)	10/18 (55.6)	<0.001
Coagulopathy	3/90 (3.3)	-	-	-	-	3/18 (16.7)	0.001
Physician-diagnosed secondary infection	21/90 (23.3)	4/59 (6.8)	1/1 (100)	<0.001	6/12 (50.0)	10/18 (55.6)	<0.001
Intubation	28/85 (32.9)	5/57 (8.8)	1/1 (100)	0.361	7/9 (77.8)	15/17 (88.2)	0.001
Presence of primary composite endpoint – no./total no. (%)‡	39/90 (43.3)	8/59 (13.6)	1/1 (100)	<0.001	12/12 (100)	18/18 (100)	<0.001
Clinical outcomes at data cutoff - no./total no. (%)†							
Discharge from hospital	66/85 (77.6)	57/57 (100)	-	<0.001	7/12 (58.3)	-	<0.001
Death	19/85 (22.4)	-	1/1 (100)	-	-	18/18 (100)	<0.001

* The denominators of patients who were included in the analysis are provided if they differed from the overall numbers in the group. Percentages may not total 100 because of rounding. IQR denotes interquartile range.

† P value less than 0.05 is considered significant.

‡ The primary composite end point was admission to an intensive care unit, the use of mechanical ventilation, or death.

§ Data for disposition were missing in 5.5% of cases.

ng/ml [IQR, 0.19-2.01] vs. 0.12 ng/ml [IQR, 0.06-0.19], $p < 0.001$) and non-severe (0.25 ng/ml vs. 0.05 ng/ml [IQR, 0.02-0.12], $p < 0.001$) categories.

CARDIAC BIOMARKERS

The median tCK level, 173.6 U/liter (IQR, 83.4-287.3) was significantly higher among non-survivors than those who survived across both categories (463.59 U/liter vs. 123.98 U/liter [IQR, 76.0-213.1], $p = 0.039$) and (178.5 U/liter [IQR, 149.4-276.6] vs. 158.7 U/liter [IQR, 115.0-193.0], $p = 0.016$).

The median hsTnI for all patients was 0.009 ng/ml (IQR, 0.004-0.026). It was significantly higher among non-survivors than those who survived for both severe (0.028 ng/ml [IQR, 0.013-0.127] vs. 0.012 ng/ml [IQR, 0.005-0.025], $p < 0.001$) and non-severe cases (0.046 ng/ml vs. 0.006 ng/ml [IQR, 0.003-0.010], $p < 0.001$). Among those with elevated hsTnI levels, the median was 0.016 ng/ml [IQR, 0.027-0.185].

No statistical significance for CK-MB isoenzyme levels across both categories was found.

COMPLICATIONS AND CLINICAL OUTCOMES

Among the non-survivors in the severe category, two (11.1%) developed ventricular tachycardia. There were four (4.4%) patients who developed new onset atrial fibrillation in the severe category and only one (5.6%) did not survive. Among the 26 patients who were in need of vasopressor support in the severe category, there were significantly more non-survivors who required vasopressors than those who survived (15, 83.3% vs. 6, 50%, $p = 0.011$). Also, of the 28 patients who were intubated in this study, 16 (57.1%) died, whereas 12 (42.9%) survived ($p = 0.001$).

Thirty-six (46.8%) individuals developed acute respiratory distress syndrome, and 16 (88.9%) in the severe category did not survive ($p < 0.001$). Acute kidney injury was noted among those who did not survive relative to those who did in the severe category (10, 55.6% vs. 6, 50%, $p < 0.001$). Among the twenty-one (23.3%) patients in the severe category who had secondary infections during the course of admission, ten (55.6%) did not

survive while six (50%) did ($p < 0.001$). At study cut off, a total of 66 (77.6%) patients were discharged from the hospital improved, while there were 19 (22.4%) who died, one (5.3%) in the non-severe and 18 (94.7%) in the severe category. The patient in the non-severe category died from brainstem failure secondary to hemorrhagic stroke.

ASSOCIATION OF CARDIAC BIOMARKERS WITH THE PRIMARY COMPOSITE ENDPOINTS AND DISEASE SEVERITY

Table 6 shows the Spearman rho correlation analysis of cardiac biomarkers with the primary composite endpoints and disease severity. There was significant weak positive association between elevated tCK levels and disease severity ($R, 0.251, p = 0.017$); ICU admission ($R, 0.357, p = 0.001$); need for intubation ($R, 0.321, p = 0.002$); and in-hospital mortality ($R, 0.313, p = 0.003$). High sensitivity troponin I had significant moderate positive association with in-hospital mortality ($R, 0.434, p < 0.001$), while it had significant weak positive association between disease severity ($R, 0.379, p < 0.001$); ICU admission ($R, 0.357, p = 0.001$); and intubation ($R, 0.346, p = 0.001$).

ASSOCIATION OF ELEVATED CARDIAC BIOMARKERS WITH IN-HOSPITAL MORTALITY

The binary logistic regression analysis for elevated cardiac biomarkers with in-hospital mortality is shown in Table 7. Univariate analysis showed that elevated levels of tCK and of hsTnI were associated with increased risk of dying. Results of the multivariate regression analysis, showed that the two cardiac biomarkers were independently associated with in-hospital mortality among COVID patients.

Figure 2 shows the ROC curve for the cardiac biomarkers with in-hospital mortality. It shows that hsTnI was a better predictor for in-hospital mortality than tCK. The ROC, cutoff and AUC of the ROC curve analysis with in-hospital mortality is shown in Table 8. At 0.015 ng/ml reference value, hs troponin I was a good significant predictor for in-hospital mortality (AUC, 0.829 [95% CI, 0.735-0.923]), $p < 0.001$, while creatine kinase was a poor significant predictor (AUC, 0.677 [95% CI, 0.531-0.823], $p = 0.018$) at 168 U/liter.

The optimal cutoff value for hsTnI of 0.010 ng/ml ($J, 0.574$; $d,$

Table 6. Spearman rho Correlation Analysis of Elevated Cardiac Biomarkers with the Primary Composite Endpoints and Disease Severity.

Cardiac Biomarkers	Disease Severity (n = 90)		ICU Admission (n = 90)		Intubation (n = 90)		Mortality (n = 90)	
	R*	Sig.†	R*	Sig.†	R*	Sig.†	R*	Sig.†
Creatine kinase	0.251	0.017	0.357	0.001	0.321	0.002	0.313	0.003
CK-MB isoenzyme	-0.033	0.755	0.029	0.786	-0.028	0.790	0.021	0.848
hs Troponin I	0.379	<0.001	0.357	0.001	0.346	0.001	0.434	<0.001

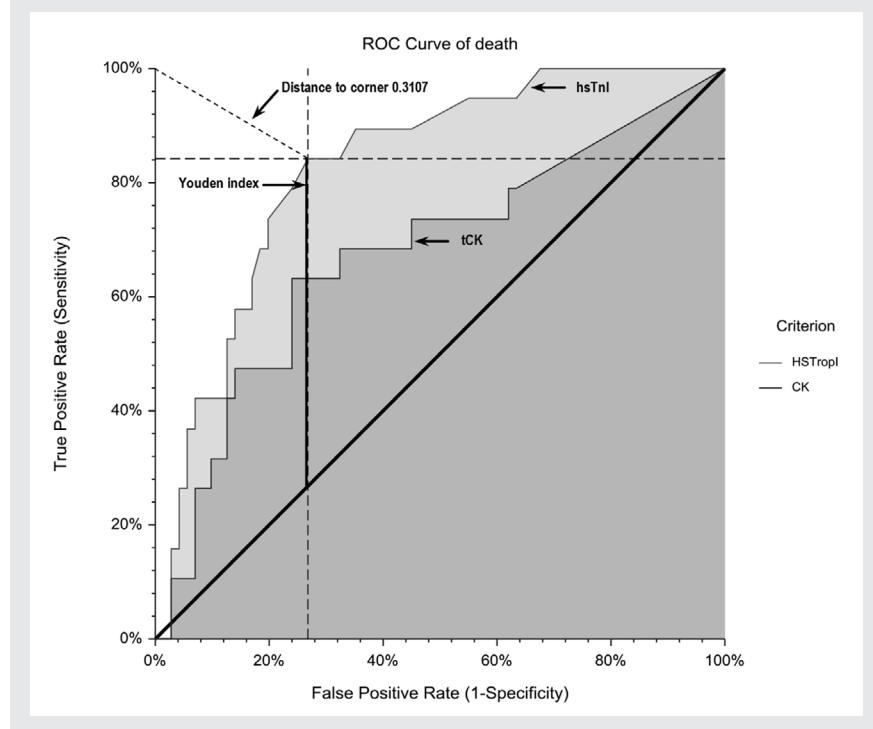
* Correlation coefficient. Interpretation, 0–0.2, very weak; 0.2–0.4, weak; 0.4–0.6, moderate; 0.6–0.8, strong; 0.8–1.0, very strong.

† P value less than 0.05 is considered significant.

Table 7. Binary Logistic Regression Analysis of the Association of Elevated Cardiac Biomarkers with Mortality Among COVID-19 Patients.

Cardiac Biomarkers	Univariate Analysis				Multivariate Analysis			
	Exp(B)	95% CI	Sig.*		Exp(B)	95% CI	Sig.*	
Creatine kinase	4.692	1.609	13.679	0.005	4.103	1.241	13.563	0.021
CK-MB isoenzyme	1.259	0.124	12.840	0.846	0.830	0.054	12.776	0.894
hs Troponin I	8.821	2.849	27.316	<0.001	7.899	2.430	25.675	0.001

* P value less than 0.05 is considered significant.

Figure 2: Receiver Operator Characteristics (ROC) Curve for Cardiac Biomarkers with In-hospital Mortality Among COVID-19 Patients.

0.311) was lower than the reference limit of 0.015 ng/ml used in this study. It had a corresponding sensitivity of 84% (TPR, 0.842 [95% CI, 0.604-0.966]), a specificity of 73% (TNR, 0.732 [95% CI, 0.614-0.831]), accuracy of 76% (0.756 [95% CI, 0.654-0.840]), a positive likelihood ratio of 3.147 (95% CI, 2.044-4.844) and a negative likelihood ratio of 0.216 (95% CI, 0.076-0.615). It had a negative predictive value of hsTnI of 95% (NPV, 0.945 [95% CI, 0.849-0.989]) which increased to 99% after adjustment to the known prevalence was done (Known prevalence*Adjusted NPV, 0.989).

In contrast, creatine kinase had a larger optimal threshold of 173 U/liter (J, 0.392; d, 0.439) than the reference limit used in this study of 168 U/liter. It had a sensitivity of 63% (TPR, 0.632 [95% CI, 0.384-0.837]), and specificity of 76% (TNR, 0.761 [95% CI, 0.645-0.854]). After adjustment to the known prevalence of COVID-19, the negative predictive value 89% (NPV, 0.885 [95% CI, 0.778-0.953]) increased to 98% (Known prevalence*adjusted NPV, 0.975).

DISCUSSION

Recent epidemiologic and clinical studies of influenza and other acute inflammatory conditions have demonstrated an association of an event leading towards acute coronary syndrome in patients with long-standing coronary artery disease and those with risk factors for atherosclerotic cardiovascular disease, i.e., diabetes, hypertension, dyslipidemia, smoking, obesity, inactive lifestyle and significant family history of heart disease.⁷⁻¹² Both severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), formerly referred to as the 2019 novel coronavirus (2019-nCoV), and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) share the same pathobiochemical and biomechanical mechanisms of myocardial damage which increase the difficulty and complexity of patient treatment.¹³

It was also shown that during acute infections, the following risk factors for atherosclerotic cardiovascular disease, like hypertension, cigarette smoking, diabetes mellitus, hyperlipidemia, and obesity, further add to the already heightened risk for acute coronary events among those with long term coronary artery disease.¹⁴⁻¹⁶

Collated data from China, Italy, and the US

Table 8. ROC Curve, Cutoff and Area Under the Curve Analysis for Elevated Cardiac Biomarkers with In-hospital Mortality Among COVID-19 Patients.

	hs Troponin I	Creatine kinase
Reference value used	0.015 ng/ml	168 U/liter
Area under the Curve (AUC)	0.829 (0.735-0.923)	0.677 (0.531-0.823)
Sig.*	< 0.001	0.018
Distance to corner (d)	0.311	0.439
Youden index (J)	0.574	0.392
Derived optimal cutoff value	0.010 ng/ml	173 U/liter
Sensitivity (TPR)	0.842 (0.604-0.966)	0.632 (0.384-0.837)
Specificity (TNR)	0.732 (0.614-0.831)	0.761 (0.645-0.854)
False positive rate	0.268 (0.169-0.386)	0.239 (0.146-0.355)
False negative rate	0.158 (0.034-0.396)	0.368 (0.163-0.616)
Positive predictive value (PPV)	0.457 (0.288-0.633)	0.414 (0.235-0.611)
Known prevalence*Adjusted PPV [‡]	0.142	0.122
Negative predictive value (NPV)	0.945 (0.849-0.989)	0.885 (0.778-0.953)
Known prevalence*Adjusted NPV [‡]	0.989	0.975
Prevalence	0.211 (0.132-0.310)	0.211 (0.132-0.310)
Accuracy	0.756 (0.654-0.840)	0.733 (0.630-0.821)
Positive likelihood ratio (LR+)	3.147 (2.044-4.844)	2.638 (1.540-4.519)
Negative likelihood ratio (LR-)	0.216 (0.076-0.615)	0.484 (0.265-0.885)
Diagnostics odds ratio	14.596 (3.821-55.766)	5.445 (1.850-16.032)

* P value less than 0.05 is considered significant.

[‡]ROC curve analysis was not done for CK-MB isoenzyme since it was not associated with in-hospital mortality.

[‡]Adjusted predictive values based on known prevalence of the disease (5%).

[§] Definitions adopted from NCSS 2020 Statistical Software (2020). NCSS, LLC, Kaysville, Utah, USA, [ncss.com/software/ncss](https://www.ncss.com/software/ncss). ³⁷Cutoff Value indicates the criterion value range that predicts a positive condition. TPR is the true positive rate or sensitivity is the proportion of the units with a known positive condition for which the predicted condition is positive. TNR is the true negative rate or specificity is the proportion of the units with a known negative condition for which the predicted condition is negative. PPV is the positive predictive value or precision is the proportion of the units with a predicted positive condition for which the true condition is positive. NPV is the negative predictive value is the proportion of the units with a predicted negative condition for which the true condition is negative. Youden Index is the Sensitivity + Specificity - 1. PPV is Distance to Corner is the distance from the top left corner of the ROC curve to the point on the ROC curve. LR+ is the positive likelihood ratio is the ratio of the true positive rate (sensitivity) to the false positive rate (1 - specificity). LR- is the negative likelihood ratio is the ratio of the false negative rate to the true negative rate (specificity). The diagnostic odds ratio is the ratio of the positive likelihood ratio to the negative likelihood ratio. The distance to the top-left corner of the ROC curve for each cutoff value is given by $d = \sqrt{(1 - sensitivity)^2 + (1 - specificity)^2}$. The accuracy reflects the total proportion of units that are correctly predicted or classified.

showed that older individuals with COVID-19 with underlying cardiovascular and other comorbidities, have a higher risk to develop adverse clinical outcomes and to mortality, as compared to those younger and healthier adults.¹⁴⁻¹⁷

Bonow et al recognized that patients with underlying cardiovascular disease which can be mostly seen in older people had more unfavorable outcomes and death during serious and aggressive inflammatory reactions to COVID-19 compared to younger and healthier individuals.¹⁸ Likewise, two cohorts demonstrated the association of myocardial injury with increased fatality rate among older patients with preexisting cardiovascular comorbidities and diabetes.¹⁹⁻²⁰

Myocardial injury is one of the more clinically significant manifestations of COVID-19. It is not yet well known how this is brought about by SARS-CoV-2 infection due to a lack of randomized controlled trials and the acuteness of this global pandemic. Current data suggest that the interaction between SARS-CoV-2 and cardiac angiotensin-converting enzyme 2 (ACE-2) receptors may precipitate myocardial damage. One of the proposed mechanisms is that cardioprotection provided by angiotensin 1-7 is hindered by the downregulation of ACE-2 receptors thereby resulting in increased inflammatory cytokines such as tumor necrosis factor-alpha (TNF α).²¹ Other hypothesized mechanisms of myocardial injury include induction of interstitial fibrosis in the myocardium by activation of TGF β -signaling by SARS-CoV-2, exaggerated cytokine response by T-Helper cells (both type 1 and type 2), as well as strong interferon-mediated immune reactions.²¹

These acute coronary events result from the severe increase in myocardial demand triggered by infections that precipitate myocardial injury or type 2 myocardial infarction.¹⁴⁻¹⁷ Additionally, during severe systemic inflammatory stress, the circulating cytokines released could also lead to atherosclerotic plaque instability and rupture.¹⁴⁻¹⁷ Wang et al postulated that the increase in metabolic demand brought about by the viral infection potentiates the imbalance and reduce the cardiac reserve thereby making chronic cardiovascular diseases unstable.¹³

Most epidemiologic studies enrolled more severe cases than non-severe ones,⁸⁻¹⁰ but in this study, there were more cases in the non-severe category than in the severe category. The findings in this study of marked elevation of acute inflammatory markers, i.e., neutrophil count, AST, serum ferritin, LDH, creatine kinase, D-dimer, and hs-CRP among subjects with COVID-19 who developed complications were all in congruence with other international and local studies.²²⁻²⁶

This study showed similar findings that older patients with co-morbid conditions were predisposed to increase adverse events.^{12, 26, 28-33} Additionally, it was shown that creatine kinase and hsTnI had a direct association with disease severity and the primary composite endpoints (ICU admission, intubation, and mortality). The strength of correlation was generally weak, except for that of hsTnI with in-hospital mortality where it was moderate. Direct correlations of both tCK and hsTnI with disease severity and the primary composite endpoints were shown in this study. These could be ascribed to the actual myocardial injury caused by the SARS-CoV-19 similar to what was observed in other previous studies.^{13, 15, 19, 20}

As with other international and local studies, this study

also demonstrated that the majority of the mortalities have acute myocardial injury as evidenced by increased levels of hsTnI.^{12, 13, 15, 20, 26, 34} The demonstration of the value of cardiac troponin to in-hospital mortality among COVID-19 patients resembles other previous investigations.^{12, 13, 15, 19, 20} Those laboratory-confirmed patients with elevated hsTnI levels were eight times more likely to succumb to the disease relative to those who did not. Also, the odds that COVID patients were more likely to die when they have elevated levels of tCK was increased four times as opposed to those who have normal levels.

The AUC analysis of the ROC curve further showed that hsTnI was a good predictor for in-hospital mortality, while creatine kinase was a poor significant predictor of in-hospital mortality. Evaluating the 95% CI showed that the lower limit of tCK was 0.531. Anything below the threshold limit of 0.6 would have no value as an instrument, hence nullifying its significance as a tool for predicting in-hospital mortality.

As with other previous studies, the severity of damage to the myocardium was reflected by the increase in hsTnI levels, where the more severe the damage, the more the patient was predisposed to adverse clinical outcome and mortality.^{12, 13, 15, 19, 20} The extent of insult might affect myocardial function which could draw hemodynamic instability anytime. Hence, the positive association of the biomarker with in-hospital mortality among patients with COVID infection existed.

Studies have shown that high specificity is one characteristic of an extremely good screening test to avoid large numbers of false positives.³⁶⁻³⁷ The cutoff analysis revealed an optimal cutoff value for hsTnI of 0.010 ng/ml in predicting myocardial injury which was directly associated with in-hospital mortality among COVID-19 patients, and it was specific to as high as 83%, and was sensitive to as high as 97% at the most. If the test was negative, one can be 99% confident that there was no myocardial injury resulting from COVID-19 infection. Seventy-six percent of those who will exceed the threshold will be correctly classified as having myocardial damage. The probability of having myocardial injury is increased by 20% when hsTnI levels exceed 0.010 ng/ml among COVID-19 patients, whereas it is decreased by 30% when hsTnI levels are below 0.010 ng/ml.

CONCLUSION

In this small study of 90 rRT-PCR positive COVID-19 patients with cardiac biomarker determinations, high sensitivity troponin I level is a good tool in significantly predicting in-hospital mortality.

LIMITATIONS

A much bigger sample size will ensure more robust conclusions. There were missing data on some of the variables, such as symptoms pre-admission (4/90, [4.4%]) and eventual disposition (5/90, [5.5%]).

KEYWORDS

Coronavirus disease-2019. COVID-19. Predictors of In-hospital mortality. Cardiac biomarkers. HS troponin I. ROC analysis. AUC analysis. Cutoff analysis.

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