SARS-CoV-2 Viral Load and Myocardial Injury: Independent and Incremental Predictors of Adverse Outcome

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Abstract

To evaluate the association of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initial viral load (iVL) and the incidence of myocardial injury (MCI) in hospitalized patients with SARS-CoV-2 infection, we conducted a retrospective longitudinal study of hospitalized patients who had a nasopharyngeal swab sample on admission that returned a positive result for SARS-CoV-2 by polymerase chain reaction between April 4 and June 5, 2020. The cycle threshold (Ct) value was used as a surrogate for the iVL level, with a Ct level of 36 or less for elevated iVL and greater than 36 for low iVL. Myocardial injury was defined as an elevated high-sensitivity cardiac troponin I level that was higher than the 99th percentile upper reference limit. A total of 270 patients were included. Of these, 171 (63.3%) had an elevated iVL and 88 (32.6%) had MCI. There was no significant difference in the incidence of MCI in patients with low iVL compared to those with elevated iVL (28 of 99 [28.3%] vs 60 of 171 [35.1%; P=.25]). In a multivariable model, MCI (odds ratio, 3.86; 95% CI, 1.80 to 8.34; P<.001) and elevated iVL (odds ratio, 4.21; 95% CI, 2.06 to 8.61; P<.001) were independent and incremental predictors of in-hospital mortality. The SARS-CoV-2 iVL level is not associated with increased incidence of MCI, although both parameters are strong independent and incremental predictors of mortality. Understanding the MCI mechanisms allows for early focused interventions to improve survival, especially in patients with SARS-CoV-2 infection and high iVL.

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Medical Center from April 4 through June 5, 2020. Patients without a serial high-sensitivity troponin I (hs-cTnI) test on admission and those transferred to our center from an outside hospital were excluded.

**Myocardial Injury**
Myocardial injury during hospitalization was defined as any hs-cTnI level greater than 100 ng/L (to convert value to μg/L, multiply by 1.0), which corresponds to a level greater than the 99th percentile of the upper reference limit (Beckman Coulter, Inc).³

**SARS-CoV-2 Viral Load**
Only the initial real-time polymerase chain reaction result was included. The cycle threshold (Ct) value can be used to estimate the number of viral particles in a patient’s sample in such a way that every 3.3 decrease in Ct value indicates a 10-fold increase in target concentration. Using a quantified standard, we found a linear relationship between viral load and Ct value over multiple “1 to 10” dilutions of standard. At 2 × 10³ and 2 × 10⁴ viral particles, the Ct values were 43 and 36.7, respectively. Based on our published research,⁸ we designated high, intermediate, and low iVL samples to have a Ct value of 25 or less, 26 to 36, and 37 or greater, respectively. Subsequently, we combined the intermediate and the high iVL categories and dichotomized the study population into the low and elevated iVL groups. The lower limit of detection of the assay used is approximately 250 genome copies per milliliter (95% confidence).

**Statistical Analyses**
Analysis was performed using SPSS Statistics for Windows, version 25 (IBM Corp), and graphical representations were created with GraphPad Prism, version 9.0.1. Continuous variables were represented by the median and interquartile range. The χ² and Fisher exact tests were used to compare categorical variables, and the Mann-Whitney U test and Student t test were used for continuous variables. A multivariable logistic regression was performed to assess predictors of mortality among patients admitted with SARS-CoV-2. Survival analysis of groups of patients stratified by viral load level and MCI was performed, and a log-rank test was deployed to identify differences between the 3 groups of interest. Statistical analyses were considered significant at P ≤ .05.

**Ethical Considerations**
The institutional review board at Wayne State University/Detroit Medical Center reviewed the study protocol, and ethical approval for the conduction of this study was granted (IRB RR19393).

**RESULTS**
A total of 454 hospitalized patients had a positive nasopharyngeal SARS-CoV-2 polymerase chain reaction result on presentation. Of these, 270 had hs-cTnI levels available; 171 patients (63.3%) had elevated iVL, 88 (32.6%) had MCI during hospitalization (Table 1), and 60 (22.2%) had both MCI and elevated viral load.

Patients with elevated iVL were older (74 vs 65 years; P < .001), more likely to reside in a nursing home facility (71 of 171 [41.5%] vs 29 of 99 [29.3%]; P = .045), and had a shorter duration from symptom onset to polymerase chain reaction results. Patients in whom MCI developed during hospitalization were older (77 vs 64 years; P = .02) and had a history of coronary artery disease (30 of 88 [34.1%] vs 33 of 182 [18.1%]; P = .004) and cerebrovascular disease (42 of 88 [47.7%] vs 59 of 182 [32.4%]; P = .015). During their hospitalization, patients with evidence of MCI had a higher rate of respiratory failure requiring intubation than patients with no MCI (42 of 88 [47.7%] vs 50 of 182 [27.5%]; P = .001). In contrast, there was no significant difference in the percentage of patients in whom respiratory failure developed among the groups with low and elevated iVL (33 of 99 [33.3%] vs 59 of 171 [34.5%], respectively; P = .8).

There was no significant difference in the incidence of MCI between low and elevated iVL groups (28 of 99 [28.3%] vs 60 of 171 [35.1%]; P = .25) (Figure 1 A) nor between low, intermediate, and high iVL groups (28 of 99 [28.3%] vs 33 of 105 [31.4%] vs 27 of 66 [40.9%], respectively; P = .22) (Figure 1 B). Similarly, there was no difference in the iVL between those with MCI and those without (G, 30.8 vs 33.15; P = .22) (Figure 1 C). No significant correlation was found between peak
### TABLE 1. Demographic and Clinical Characteristics and Laboratory Results of Hospitalized Patients With SARS-CoV-2 Infection

| Variable                          | Overall (N=270) | Without (n=182 [67.4]) | With (n=88 [32.6]) | P value | Low (n=99 [36.7]) | Elevated (n=171 [63.3]) | P value |
|-----------------------------------|-----------------|------------------------|---------------------|---------|------------------|-------------------------|---------|
| **Demographic characteristic**   |                 |                        |                     |         |                  |                         |         |
| Age (y)                           | 70 (57-78)      | 64 (51-81.75)          | 77 (74-84)          | .02     | 65 (50-78)       | 74 (62.25-84.50)        | <.001   |
| 18-39                             | 11 (4.1)        | 6 (3.3)                | 5 (5.7)             | .04     | 6 (6.1)          | 5 (2.9)                 | <.001   |
| 40-65                             | 95 (35.2)       | 73 (40.1)              | 22 (25.0)           |         | 48 (48.5)        | 47 (27.5)               |         |
| >65                               | 164 (60.7)      | 103 (56.6)             | 61 (69.3)           |         | 45 (45.5)        | 119 (69.6)              |         |
| **Sex**                           |                 |                        |                     |         |                  |                         |         |
| Female                            | 132 (48.9)      | 91 (50.0)              | 41 (46.6)           |         | 46 (46.5)        | 86 (50.3)               | .5      |
| Male                              | 138 (51.1)      | 91 (50.0)              | 47 (53.4)           |         | 53 (53.5)        | 85 (49.7)               |         |
| **Race**                          |                 |                        |                     |         |                  |                         |         |
| White                             | 23 (8.5)        | 18 (9.9)               | 5 (5.7)             | .2      | 5 (5.1)          | 18 (10.5)               | .3      |
| Black                             | 210 (77.8)      | 136 (74.7)             | 74 (84.1)           |         | 80 (80.8)        | 130 (76.0)              |         |
| Other                             | 37 (13.7)       | 28 (15.4)              | 9 (10.2)            |         | 14 (14.1)        | 23 (13.5)               |         |
| **Body mass index (kg/m²)**       | 30.0 (25.3-40.8)| 29.15 (25.07-39.72)    | 29.80 (21.65-39.15) | .07     | 29.80 (25.00-40) | 27.85 (21.87-40.85)     | .2      |
| <18                               | 6 (2.2)         | 3 (1.6)                | 3 (3.4)             | .2      | 2 (2.0)          | 4 (2.3)                 | .8      |
| 18-30                             | 68 (25.2)       | 40 (22.0)              | 28 (31.8)           |         | 22 (22.2)        | 46 (26.9)               |         |
| 30-40                             | 82 (30.4)       | 60 (33.0)              | 22 (25.0)           |         | 31 (31.3)        | 51 (29.8)               |         |
| >40                               | 114 (42.2)      | 79 (43.4)              | 35 (39.8)           |         | 44 (44.4)        | 70 (40.9)               |         |
| Residing in a nursing home/facility | 100 (37.0)   | 63 (34.6)              | 37 (42.0)           | .2      | 29 (29.3)        | 71 (41.5)               | .045    |
| **Symptoms at admission**         |                 |                        |                     |         |                  |                         |         |
| Days from onset of symptoms to RT-PCR results | 0-7 | 209 (77.4) | 139 (76.4) | 70 (79.5) | .6 | 63 (63.6) | 146 (85.4) | <.001 |
|                                   | >7              | 61 (22.6)              | 43 (23.6)           | 18 (20.5) | 36 (36.4) | 25 (14.6) |         |
| GI symptoms                       | 67 (24.8)       | 56 (30.8)              | 11 (12.5)           | .001    | 26 (26.3)        | 41 (24.0)               | .7      |
| Upper/lower respiratory tract symptoms | 195 (72.2) | 131 (72.0) | 64 (72.7) | .8 | 67 (67.7) | 128 (74.9) | .25 |
| Neurologic symptoms               | 109 (40.4)      | 70 (38.5)              | 39 (44.3)           | .4      | 43 (43.4)        | 66 (38.6)               | .4      |
| **Systemic symptoms**             |                 |                        |                     |         |                  |                         |         |
| Heart rate (bpm)                  | 93 (82-108)     | 93 (82-107)            | 96 (82-112)         | .1      | 91 (79-105)      | 94 (82-109)             | .1      |
| Respiratory rate (breaths/min)    | 20 (18-24)      | 20 (18-24)             | 22 (18-24)          | .008    | 19 (18-22)       | 22 (18-26)              | .006    |
| Mean arterial pressure (mm Hg)    | 89 (78-103)     | 96 (78-104)            | 85 (76-97)          | .1      | 92 (80-104)      | 86 (76-101)             | .03     |
| Temperature (°C)                  | 37.0 (36.6-37.7)| 37.0 (36.6-37.7)       | 36.9 (36.4-38.0)    | .3      | 36.9 (36.6-37.4) | 37.0 (36.5-38.0)        | .1      |

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| Variable                          | Overall (N=270) | Myocardial injury | Initial viral load | P value | P value |
|----------------------------------|-----------------|-------------------|--------------------|---------|---------|
|                                  | Without (n=182 [67.4]) | With (n=88 [32.6]) | Low (n=99 [36.7]) | Elevated (n=171 [63.3]) |
| Comorbidities                    |                 |                   |                    |         |         |
| Hypertension                     | 212 (78.5)      | 143 (78.6)        | 69 (78.4)          | >.99    | 79 (79.8) |
| Diabetes mellitus                | 122 (45.2)      | 83 (45.6)         | 39 (44.3)          | .8      | 47 (47.5) |
| Congestive heart failure         | 60 (22.2)       | 23.9 (88)         | 39 (21.4)          | .65     | 20 (20.2) |
| Coronary artery disease          | 63 (23.3)       | 33 (18.1)         | 30 (34.1)          | .004    | 23 (23.2) |
| Atrial fibrillation/flutter       | 35 (13.0)       | 21 (11.5)         | 14 (15.9)          | .3      | 13 (13.1) |
| Any cardiovascular disease       | 101 (37.4)      | 59 (32.4)         | 42 (47.7)          | .015    | 33 (33.3) |
| Cerebrovascular disease          | 53 (19.9)       | 33 (18.1)         | 20 (22.7)          | .2      | 37 (37.4) |
| Chronic kidney disease           | 74 (27.4)       | 54 (29.7)         | 20 (22.7)          | .1      | 37 (21.6) |
| Smoking history                  | 50 (18.5)       | 14 (15.9)         | 36 (19.8)          | .4      | 17 (17.2) |
| Chronic obstructive pulmonary disease | 17 (6.3)     | 9 (49)            | 8 (9.1)            | .2      | 5 (5.1) |
| Asthma                           | 45 (16.7)       | 30 (16.5)         | 15 (17.0)          | .9      | 14 (14.1) |
| Immunosuppression                |                 |                   |                    |         |         |
| Laboratory data                  |                 |                   |                    |         |         |
| Creatinine (mg/dL)               | 2.67 (1.11-4.37) | 2.94 (1.21-7.54)  | 2.51 (1.06-3.56)   | .003    | 4.30 (1.789) |
| White blood cell count (K/µL)    | 8200 (5350-10,700) | 6250 (4550-10,100) | 7200 (4950-14,350) | <.001   | 5700 (5000-10,800) |
| Neutrophil count (K/µL)          | 6100 (3150-8900) | 5050 (2275-8425)  | 6100 (3950-12,900) | <.001   | 4100 (2200-9000) |
| Lymphocyte count (K/µL)          | 700 (450-1050)   | 700 (425-1075)    | 600 (400-800)      | .1      | 600 (400-1300) |
| Platelet count (K/µL)            | 200,000 (162,500-234,500) | 234,500 (180,500-335,000) | 186,000 (123,000-283,500) | .7 | 214,000 (151,000-239,000) |
| Aspartate aminotransferase (IU/L) | 33 (21.5-43.5)   | 27 (17.75-45.25)  | 36 (29-217)        | .008    | 25 (20-77) |
| Alanine aminotransferase (IU/L)  | 20.0 (11.0-33.5) | 17.5 (10.33-75)   | 17 (11-1125)       | .05     | 15 (10-31) |
| Total bilirubin (mg/dL)          | 0.68 (0.42-1.11) | 0.61 (0.38-0.945) | 0.94 (0.37-1.94)   | .4      | 0.90 (0.59-0.96) |
| Lactate dehydrogenase (IU/L)     | 47.1 (219.5-700.5) | 374.50 (222.25-532) | 422 (348.5-1159) | .002    | 471 (232-728) |
| C-reactive protein (mg/dL)       | 112.59 (59.13-168) | 68.7 (10.89-171)  | 112.59 (73.63-152.16) | .003   | 69.87 (17-174) |
| Ferritin (ng/mL)                 | 421.30 (264.45-717.05) | 370.40 (212.5-673.42) | 726.10 (462.95-1152) | <.001  | 421.30 (250-1124.10) |
| D-dimer (µg/mL)                  | 2.75 (1.17-22.0) | 37 (1.17-14.75)   | 1.35 (0.62-20.40)  | .005    | 2.75 (2.07-35.20) |

*abpm, beats per minute; GI, gastrointestinal tract; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

#SI conversion factors: To convert creatinine values to $\text{m}^2\text{mol/L}$, multiply by 88.4; to convert white blood cell, neutrophil, and lymphocyte counts to $\times 10^9/\text{L}$, multiply by 0.001; to convert aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase values to $\text{m}^2\text{kat/L}$, multiply by 0.0167; to convert ferritin values to $\text{pmol/L}$, multiply by 0.001; to convert D-dimer values to $\text{nmol/L}$, multiply by 5.476.
troponin levels and Ct value (Spearman correlation coefficient of −0.09 and \(P=1\)).

Using a multivariable logistic regression model, MCI (odds ratio [OR], 4.21; 95% CI, 2.06 to 8.61; \(P<.001\)), elevated viral load (OR, 3.86; 95% CI, 1.80 to 8.34; \(P<.001\)), acute kidney injury (OR, 2.49; 95% CI, 1.16 to 5.32; \(P=.02\)), and acute respiratory distress syndrome (OR, 8.48; 95% CI, 3.85 to 18.64; \(P<.001\)) were identified as significant independent predictors of mortality (Table 2).

The survival analysis curves (Figure 2) illustrate a decrease in survival in the presence of either cardiac injury or elevated viral load and a further decrease with the simultaneous presence of both MCI and elevated viral load (log-rank \(P<.001\)). Patients who had both an elevated viral load on presentation and MCI had the worst prognosis, with only about 40% survival at 30-day follow-up.

**DISCUSSION**

Our study revealed no association between cardiac injury and elevated viral load. However, it was possible to risk-stratify patients with SARS-CoV-2 infection into 3 distinct groups based on survival rates, with the worst outcomes in those with simultaneous MCI and elevated viral load.

Cardiac injury is common among patients with SARS-CoV-2 infection, although its pathogenesis is not yet fully understood. Various, but often overlapping, mechanisms of cardiac injury in SARS-CoV-2–infected patients have been proposed, including oxygen supply-demand imbalance, direct invasion of the myocardium, inflammation, microvascular thrombosis, plaque rupture, and stress cardiomyopathy.

The mechanism of SARS-CoV-2 invasion and intracellular replication is facilitated by the binding of the viral envelope S protein to the angiotensin-converting enzyme 2 receptor on the host cell membrane, a transmembrane protein that is expressed in lung, blood vessels, heart, kidneys, and intestines. This process is followed by viral entry into the cell, triggering a cascade of events leading to viral replication and eventual release from the cell.

**TABLE 2. Predictors of In-Hospital Mortality in Patients With SARS-CoV-2 Infection on Multivariable Logistic Regression**

| Variable                        | Odds ratio (95% CI) | \(P\) value |
|---------------------------------|---------------------|-------------|
| Elevated viral load            | 3.86 (1.80-8.34)    | <.001       |
| Acute renal injury              | 2.49 (1.16-5.32)    | .02         |
| Myocardial injury               | 4.21 (2.06-8.61)    | <.001       |
| Acute respiratory distress syndrome | 8.48 (3.85-18.64)  | <.001       |

*Variables also include age, days from onset of symptoms to real-time polymerase chain reaction results, peak D-dimer level, and history of immunosuppression.
autopsies in patients with SARS-CoV-2 infection revealed that the virus can reside in cardiomyocytes even in the absence of clinical and laboratory evidence of cardiac injury. Common histopathologic findings included intracellular edema, thrombi and neutrophilic plugs, and interstitial macrophage infiltration. In one study, SARS-CoV-2–infected cells were only sporadically present in cardiomyocytes at later stages of the infection, suggesting that a maladaptive immune response rather than direct tissue infection is responsible for end-organ damage seen in affected patients. This suggestion was echoed by Duerr et al, who supported an association between hyperinflammation and myocardial damage in SARS-CoV-2 infection, with higher CD8 regulatory T-cell/monocyte ratios seen in patients who experienced respiratory failure or died.

Our study was limited by its average sample. Additionally, since the objective of the study was to examine the association between the viral load level and MCI, time to hs-cTnI levels greater than 100 ng/L was not assessed. This issue may affect the generalizability of our findings and their applicability to different situations. Finally, viral load levels were estimated in specimens collected using nasopharyngeal swabs, which likely represent the most employed diagnostic modality for SARS-CoV-2 infection. Although a recent study found a significantly higher rate of MCI in patients with higher viremia or viral load in the blood (76% vs 37%; P < .0004), our study did not find such an association using swab samples. It remains unclear to what extent viral load levels in the blood and the nasopharyngeal specimens correlate.

CONCLUSION
There is no association between elevated SARS-CoV-2 viral load and MCI. However, both parameters are strong independent and incremental predictors of mortality in symptomatic patients with SARS-CoV-2 infection. A better understanding of the MCI mechanisms may lead to early tailored interventions to improve survival in patients with SARS-CoV-2 infection, especially in those with higher viral load.

Abbreviations and Acronyms: Ct, cycle threshold; hs-cTnI, high-sensitivity troponin I; iVL, initial viral load; MCI, myocardial injury; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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