Myocardial injury in hospitalized COVID-19 patients: a retrospective study, systematic review, and meta-analysis

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Abstract

Introduction: The majority of studies evaluating the effect of myocardial injury on the survival of COVID-19 patients have been performed outside of the United States (U.S.). These studies have often utilized definitions of myocardial injury that are not guideline-based and thus, not applicable to the U.S. patient population.

Methods: The current study is a two-part investigation of the effect of myocardial injury on the clinical outcome of patients hospitalized with COVID-19. The first part is a retrospective analysis of 268 patients admitted to our healthcare system in Toledo, Ohio, U.S.; the second part is a systematic review and meta-analysis of all similar studies performed within the U.S.

Results: In our retrospective analysis, patients with myocardial injury were older (mean age 73 vs. 59 years, \( P < 0.001 \)), more likely to have hypertension (86% vs. 67%, \( P = 0.005 \)), underlying cardiovascular disease (57% vs. 24%, \( P < 0.001 \)), and chronic kidney disease (26% vs. 10%, \( P = 0.004 \)). Myocardial injury was also associated with a lower likelihood of discharge to home (35% vs. 69%, \( P < 0.001 \)), and a higher likelihood of death (33% vs. 10%, \( P < 0.001 \)), acute kidney injury (74% vs. 30%, \( P < 0.001 \)), and circulatory shock (33% vs. 12%, \( P < 0.001 \)). Our meta-analysis included 12,577 patients from 8 U.S. states and 55 hospitals who were hospitalized with COVID-19, with the finding that myocardial injury was significantly associated with increased mortality (HR 2.43, CI 2.28–3.6, \( P < 0.0005 \)). The prevalence of myocardial injury ranged from 9.2 to 51%, with a mean prevalence of 27.2%.

Conclusion: Hospitalized COVID-19 patients in the U.S. have a high prevalence of myocardial injury, which was associated with poorer survival and outcomes.

Introduction

The COVID-19 pandemic continues to affect millions of people in the United States (U.S.) and across the world [1]. Myocardial injury, as reflected by an increase in the serum troponin level above the 99th percentile, has been found to be relatively common in hospitalized COVID-19 patients and may predict a poor prognosis. However, most of these studies have been performed outside of the U.S. [2–4] and utilize definitions of myocardial injury that are not guideline-based, thus making it difficult to apply such findings to the hospitalized COVID-19 population within the U.S. [5–7]. The goal of the present study is to determine the prevalence of myocardial injury in the hospitalized COVID-19 patient population in the U.S., compare outcomes with hospitalized patients who have COVID-19 without myocardial injury, and to determine the risk factors for the development of myocardial injury.
and possible differences in clinical outcome between the two groups. In addition, we carry out a systematic review of current U.S. studies, summarize their findings, and perform a meta-analysis.

**Methods**

This study has two parts: one is a retrospective analysis of patients admitted to our health system; the second is a systematic review and meta-analysis of all similar studies performed in the U.S.

We conducted a retrospective study of a hospitalized patient population at two tertiary care hospitals in Toledo, Ohio, U.S. Adult (>18 years) patients who were hospitalized with the diagnosis of COVID-19 from 1 January 2020 through 1 May 2020 were included. Patients with type 1, 3, 4, and 5 myocardial infarctions were excluded from the study. Real-Time RT-PCR (cobas® SARS-CoV-2 Test) was used to establish COVID-19 diagnosis via nasopharyngeal and oropharyngeal swab samples obtained from our patients.

Myocardial injury was defined using the fourth universal definition of myocardial infarction as below:

Detection of a rise and/or fall of cTn with at least one value above the 99th percentile (in our laboratory this a troponin I > 0.04 ng/ml) and myocardial oxygen supply and demand mismatch not related to coronary thrombosis, with a minimum of one of the following: clinical symptoms related to cardiac ischemia; electrocardiographic changes suggestive of ischemia; new and pathological Q waves; imaging suggestive of acute loss of viable myocardium, or incident regional wall motion abnormalities consistent with ischemia [8].

All hospitalized COVID-19 patients received an EKG on admission. The present study only included patients who had serum troponin levels checked, which was based on clinical suspicion and/or EKG or imaging abnormalities. Eleven patients were excluded from the study as serum troponin was not measured in their cases.

Data were collected by review of individual electronic medical records from the hospital database. Data were collected on demographics, baseline comorbidities, hospital course, clinical and laboratory variables, cost, and outcomes. The underlying cardiovascular disease (CVD) status was identified by review of patient charts. To qualify for the CVD group, patients needed to have at least one of the following diagnoses: ischemic heart disease, congestive heart failure, and/or atrial fibrillation.

The statistics were performed using Statistical Package for the Social Sciences (SPSS), Version 20.0. We used mean, standard deviation/standard error of mean, and percentage when appropriate for the patient’s characteristic description. Group differences were compared using the Pearson $\chi^2$ or Fisher’s exact test for categorical variables, or the Student $t$ test for continuous variables. $P$ values < 0.05 were regarded as significant. We conducted univariate and multivariate regression analysis for factors contributing to myocardial injury, and for the effect of myocardial injury on different outcomes. The variables with statistical significance on univariate analysis were analyzed with multivariate analysis. Multivariate analysis was performed separately for clinical factors (4 variables) and for hospital course/clinical outcomes (4 variables).

The Institutional Review Board of Promedica Health System in Toledo, Ohio, U.S. approved the current study.

Review and meta-analysis were performed using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The study methodology is described in the Additional file 1. We exclusively included studies performed in the U.S. We searched multiple databases using keywords such as “myocardial injury”, “troponin”, and “COVID-19”. A systematic review was performed. Quantitative meta-analysis was performed only on studies that had clear outcomes defined. One study was excluded as it included only pregnant patients. We used hazard ratio (HR) and corresponding 95% confidence interval (CI) for measuring mortality outcomes. Meta-analysis was performed using Review Manager Version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, 2014), R version 3.6.2.

**Results**

A total of 268 patients were included in this study at our health system in Toledo, Ohio, U.S. Fifty-eight (22.4%) patients met the inclusion criteria of myocardial injury, and 210 patients were included in the no myocardial injury group. Baseline characteristics are described in Table 1. Patients with myocardial injury were older (mean age 73 vs. 59 years, $P$ 0.001), more likely to have hypertension (86% vs. 67%, $P$ 0.005), underlying cardiovascular disease (57% vs. 24%, $P$ 0.001), ischemic heart disease (35% vs. 16%, $P$ 0.003), heart failure with reduced ejection fraction (21% vs. 7%, $P$ 0.005), chronic kidney disease (26% vs. 10%, $P$ 0.004), and end-stage renal disease (12% vs. 2%, $P$ 0.003).

No significant statistical difference was noticed for sex, race, history of diabetes mellitus, active cancer, chronic liver disease, or home ACE inhibitor or Angiotensin II receptor blocker therapy. Patients in the myocardial injury group were less likely to initially present with fever (40% vs. 58%, $P$ 0.022), dry cough (47% vs. 68%, $P$ 0.005), or myalgias (9% vs. 27%, $P$ 0.006). Serum troponins were measured in 97% of patients hospitalized for COVID-19.

Table 2 describes the effect of myocardial injury on hospital course and clinical outcomes. Patients with
### Table 1  Patient characteristics and comorbidities; comparison of patients with and without myocardial injury

| Baseline characteristics | All patients (N = 268) | Myocardial injury (N = 58) | No myocardial injury (N = 210) | P value |
|--------------------------|------------------------|-----------------------------|-------------------------------|---------|
| **Age**                  | 62 ± 17                | 73 ± 14                     | 59 ± 17                       | <0.001  |
| **Sex**                  |                        |                             |                               |         |
| Male, n (%)              | 139 (52)               | 30 (52)                     | 109 (52)                      | 1.000   |
| Female, n (%)            | 129 (48)               | 28 (48)                     | 101 (48)                      |         |
| **Race**                 |                        |                             |                               |         |
| Caucasian, n (%)         | 172 (64)               | 43 (74)                     | 129 (62)                      | 0.176   |
| African–American, n (%)  | 80 (30)                | 13 (22)                     | 67 (32)                       |         |
| Latino, n (%)            | 13 (5)                 | 1 (1)                       | 12 (6)                        |         |
| Other, n (%)             | 2 (1)                  | 1 (1)                       | 1 (1)                         |         |
| **Hypertension, n (%)**  | 191 (71)               | 50 (86)                     | 141 (67)                      | 0.005   |
| **Diabetes mellitus, n (%)** | 97 (36)               | 24 (41)                     | 73 (35)                       | 0.359   |
| **Cardiovascular disease, n (%)** | 84 (31)               | 33 (57)                     | 51 (24)                       | <0.001  |
| **Ischemic heart disease, n (%)** | 53 (20)               | 20 (35)                     | 33 (16)                       | 0.003   |
| HFrEF, n (%)             | 13 (5)                 | 7 (12)                      | 6 (3)                         | 0.009   |
| HfprEF, n (%)            | 26 (10)                | 11 (19)                     | 15 (7)                        | 0.012   |
| **Atrial fibrillation, n (%)** | 27 (10)               | 12 (21)                     | 15 (7)                        | 0.005   |
| **Active cancer, n (%)** | 11 (4)                 | 1 (2)                       | 10 (5)                        | 0.466   |
| **Stroke, n (%)**        | 33 (12)                | 16 (28)                     | 17 (8)                        | <0.001  |
| Chronic kidney disease, n (%) | 36 (13)               | 15 (26)                     | 21 (10)                       | 0.004   |
| **ESRD on HD, n (%)**    | 11 (4)                 | 7 (12)                      | 4 (2)                         | 0.003   |
| Chronic liver disease, n (%) | 13 (5)                 | 3 (5)                       | 10 (5)                        | 1.000   |
| **Immunosuppressive state, n (%)** | 17 (6)                 | 7 (12)                      | 10 (5)                        | 0.064   |
| **Home med: ACEi, n (%)** | 60 (23)                | 15 (26)                     | 45 (22)                       | 0.297   |
| **Home med: ARBs/ARNI, n (%)** | 31 (12)                | 5 (9)                       | 26 (12)                       | 0.496   |
| Presenting vital signs   |                        |                             |                               |         |
| Heart rate               | 93 ± 19                | 92 ± 23                     | 93 ± 17                       | 0.686   |
| Respiratory rate         | 22 ± 6                 | 24 ± 8                      | 22 ± 6                        | 0.104   |
| Systolic blood pressure  | 127 ± 21               | 123 ± 22                    | 128 ± 21                      | 0.158   |
| Reasons for hospitalization |                        |                             |                               |         |
| Chest pain, n (%)        | 49 (18)                | 7 (12)                      | 42 (20)                       | 0.185   |
| Palpitations, n (%)      | 4 (2)                  | 2 (4)                       | 2 (1)                         | 0.192   |
| Fever, n (%)             | 142 (54)               | 22 (40)                     | 120 (58)                      | 0.022   |
| Malaise, n (%)           | 120 (46)               | 21 (38)                     | 99 (48)                       | 0.224   |
| Dry Cough, n (%)         | 167 (64)               | 26 (47)                     | 141 (68)                      | 0.005   |
| Anorexia, n (%)          | 39 (15)                | 4 (7)                       | 35 (17)                       | 0.089   |
| Myalgia, n (%)           | 60 (23)                | 5 (9)                       | 55 (27)                       | 0.006   |
| Dyspnea, n (%)           | 215 (82)               | 44 (80)                     | 171 (83)                      | 0.690   |
| Orthopnea, n (%)         | 1 (0.4)                | 0 (0)                       | 1 (0.5)                       | 1.000   |
| Expectoration, n (%)     | 24 (9)                 | 4 (7)                       | 20 (10)                       | 0.794   |
| Diarrhea, n (%)          | 66 (25)                | 8 (15)                      | 58 (28)                       | 0.054   |
| Headache, n (%)          | 40 (15)                | 4 (7)                       | 36 (18)                       | 0.090   |
| Vomiting, n (%)          | 37 (14)                | 6 (11)                      | 31 (15)                       | 0.519   |
| Abdominal pain, n (%)    | 23 (9)                 | 6 (11)                      | 17 (8)                        | 0.592   |

**HFpEF** congestive heart failure with preserved ejection fraction, **HFrEF** congestive heart failure with reduced ejection fraction, **EF > 50%**. There were 3 patients with HfmrEF (EF 40–50%) and were included in HfrEF group. **ESRD on HD** = End stage renal disease on hemodialysis. **Immunosuppressive state** anyone on chronic immunomodulatory drugs or with immunodeficiencies such as HIV, **ARNI** angiotensin receptor-neprilysin inhibitor, **EKG** electrocardiogram
# Table 2

| Clinical course/outcome                      | All patients (N = 268) | Myocardial injury (N = 58) | No myocardial injury (N = 210) | P value |
|----------------------------------------------|------------------------|---------------------------|--------------------------------|---------|
| Longest QTc measurement (ms)                 | 446 ± 37               | 457 ± 37                  | 443 ± 36                       | 0.008   |
| Cardiac arrest, n (%)                        | 1 (0.4)                | 0                         | 1 (0.5)                        | 1.000   |
| EKG and cardiac rhythm abnormalities         |                        |                           |                                |         |
| Arrhythmia, n (%)                            | 30 (11)                | 16 (28)                   | 14 (7)                         | <0.001  |
| Atrial fibrillation, n (%)                   | 24 (9)                 | 11 (19)                   | 13 (6)                         | 0.007   |
| Sustained VT, n (%)                          | 3 (1)                  | 2 (3)                     | 1 (0.5)                        | 0.119   |
| VT, n (%)                                     | 4 (1.5)                | 2 (3)                     | 2 (1)                          | 0.205   |
| 1st degree heart block, n (%)                | 6 (2)                  | 2 (3)                     | 4 (2)                          | 0.613   |
| 2nd (Type 2) or 3rd degree heart block, n (%)| 2 (1)                  | 0 (0)                     | 2 (1)                          | 1.000   |
| New left or right bundle branch block, n (%) | 23 (9)                 | 4 (7)                     | 19 (9)                         | 0.793   |
| ST depression or T wave inversion, n (%)     | 36 (14)                | 13 (22)                   | 23 (11)                        | 0.031   |
| ST elevation, n (%)                          | 5 (2)                  | 3 (5)                     | 2 (1)                          | 0.069   |
| QT prolongation                              | 66 (25)                | 21 (36)                   | 45 (21)                        | 0.025   |
| Abnormal EKG, n (%)                          | 99 (37)                | 35 (60)                   | 64 (30)                        | <0.001  |
| Any arrhythmia, n (%)                        | 39 (15)                | 17 (29)                   | 22 (11)                        | 0.001   |
| Troponin I peak (ng/mL)                      | 0.34 ± 1.50            | 1.48 ± 2.97               | 0.02 ± 0.02                    | <0.001  |
| Abnormal BNP, n (%)                          | 45 (30)                | 22 (56)                   | 23 (21)                        | <0.001  |
| BNP peak (pg/mL)                             | 185 ± 299              | 373 ± 411                 | 189 ± 22                       | <0.001  |
| High d-dimer, n (%)                          | 184 (72)               | 47 (84)                   | 137 (69)                       | 0.028   |
| D-dimer peak (ng/mL)                         | 3254 ± 8868            | 5854 ± 12,899             | 2640 ± 7482                    | 0.022   |
| Acute kidney injury, n (%)                   | 107 (40)               | 43 (74)                   | 64 (30)                        | <0.001  |
| Peak creatinine (mg/dL)                      | 1.85 ± 2.15            | 3.10 ± 3.46               | 1.51 ± 1.49                    | <0.001  |
| New HD or CVVHD, n (%)                       | 6 (2)                  | 1 (2)                     | 5 (2)                          | 1.000   |
| Invasive ventilation, n (%)                  | 50 (19)                | 13 (22)                   | 37 (18)                        | 0.447   |
| Shock of any type, n (%)                     | 44 (16)                | 19 (33)                   | 25 (12)                        | <0.001  |
| ARDS, n (%)                                  | 41 (15)                | 11 (19)                   | 30 (14)                        | 0.407   |
| Ischemic Stroke, n (%)                       | 2 (1)                  | 1 (2)                     | 1 (0.5)                        | 0.382   |
| DVT and/or PE, n (%)                         | 10 (4)                 | 4 (7)                     | 6 (3)                          | 0.228   |
| Death, n (%)                                 | 41 (15)                | 19 (33)                   | 22 (10)                        | <0.001  |
| Discharge                                    |                        |                           |                                |         |
| Home, n (%)                                  | 165 (62)               | 20 (35)                   | 145 (69)                       | <0.001  |
| SNF, n (%)                                   | 59 (22)                | 17 (29)                   | 42 (20)                        |         |
| LOS (days)                                   | 9 ± 9                  | 9 ± 10                    | 9 ± 9                          | 0.866   |
| Cost of hospitalization (US dollars)         | 92,727 ± 125,821       | 84,271 ± 104,119          | 95,535 ± 131,126               | 0.547   |
| In hospital medications                     |                        |                           |                                |         |
| Hydroxychloroquine, n (%)                    | 187 (70)               | 37 (65)                   | 150 (72)                       | 0.329   |
| Azithromycin, n (%)                          | 40 (15)                | 10 (18)                   | 30 (14)                        | 0.536   |
| Hydroxychloroquine AND Azithromycin, n (%)   | 33 (12)                | 8 (14)                    | 25 (12)                        | 0.654   |
| Tobilizumab, n (%)                           | 6 (2)                  | 0 (0)                     | 6 (3)                          | 0.346   |
| > 1 QT prolonging drug, n (%)                | 139 (52)               | 30 (53)                   | 109 (52)                       | 1.000   |
| Therapeutic anticoagulation, n (%)           | 23 (9)                 | 10 (18)                   | 13 (6)                         | 0.025   |
| Steroids, n (%)                              | 41 (15)                | 18 (32)                   | 23 (11)                        | <0.001  |
| ACEi/ARB, n (%)                              | 40 (15)                | 5 (9)                     | 35 (17)                        | 0.149   |
| ARBs, n (%)                                  | 31 (12)                | 2 (3)                     | 29 (14)                        | 0.035   |

Abnormal D-dimer was defined by more than the lab specified value of 255 ng/mL. High troponin was defined by a value more than the lab specified value of 0.04 ng/mL. QTc was considered prolonged if more than 460 ms in men and more than 480 ms in women on any EKG done during hospital stay.

SI units for BNP = pg/mL. Abnormal BNP was defined by a value of more than 100 pg/mL.

Units for creatinine = mg/dL.

Units for troponin I = ng/mL.
myocardial injury were more likely to have QT prolongation (36% vs. 21%, \(P = 0.025\)), with longer QTc measurements (457 ms vs. 443 ms, \(P = 0.008\)), and abnormal EKG readings (60% vs. 30%, \(P = 0.001\)), with greater likelihood of having arrhythmias (28% vs. 7%, \(P = 0.001\)), atrial fibrillation (19% vs. 6%, \(P = 0.007\)), ST depression or T wave inversion (22% vs. 11%, \(P = 0.031\)). Patients with myocardial injury were also more likely to have abnormal BNP (56% vs. 23%, \(P = 0.001\)), elevated D-dimer (84% vs. 69%, \(P = 0.028\)) with higher D-dimer peak (5854 vs. 2640, \(P = 0.022\)), acute kidney injury (74% vs. 30%, \(P = 0.001\)), and circulatory shock (33% vs. 12%, \(P = 0.001\)). Patients with myocardial injury had a lower likelihood of discharge to home (35% vs. 69%, \(P = 0.001\)) and a higher likelihood of death (33% vs. 10%, \(P = 0.001\)). Patients with myocardial injury were more likely to have received therapeutic anticoagulation (18% vs. 6%, \(P = 0.025\)), steroid therapy (32% vs. 11%, \(P = 0.001\)), and less likely to have received angiotensin II receptor blocker therapy during their hospital course (3% vs. 14%, \(P = 0.035\)). There was no association between myocardial injury and length of stay or cost of hospitalization.

Univariate and Multivariate regression analysis were performed as detailed in Table 3. On univariate analysis, the odds of having myocardial injury were higher with age (OR 1.06, 95% CI 1.04–1.08), hypertension (OR 3.06, 95% CI 1.37–6.81), underlying cardiovascular disease (OR 4.12, 95% CI 2.24–7.56), ischemic heart disease (OR 2.82, 95% CI 1.46–5.44), congestive heart failure with reduced ejection fraction (OR 4.67, 95% CI 1.50–14.49), congestive heart failure with preserved ejection fraction (OR 3.04, 95% CI 1.31–7.05), atrial fibrillation (OR 3.39, 95% CI 1.49–7.73), and end stage renal disease (OR 7.07, 95% CI 1.99–25.07). The odds of having myocardial injury were also higher with abnormal EKG (OR 3.47, 95% CI 1.90–6.34), and EKG findings of arrhythmia (OR 5.46, 95% CI 2.47–12.07), atrial fibrillation (OR 3.53, 95% CI 1.49–8.37), ST depression or T wave inversion (OR 2.34, 95% CI 1.09–4.97), and QT prolongation (OR 2.08, 95% CI 1.11–3.90). Additionally, the odds of having myocardial injury were also higher with abnormal BNP (OR 4.95, 95% CI 2.27–10.82), high D-dimer (OR 2.40, 95% CI 1.11–5.20), acute kidney injury (OR 3.39, 95% CI 3.39–12.62), shock of any type (OR 3.70, 95% CI 1.85–7.39), do not resuscitate & comfort care status (OR 4.66, 95% CI 2.49–8.71), discharge to skilled nursing facility (OR 2.94, 95% CI 1.41–6.10), and death (OR 4.25, 95% CI 2.09–8.61). On multivariate analysis, the association of myocardial injury with age, underlying cardiovascular disease, end stage renal disease, arrhythmia on EKG, abnormal BNP, and acute kidney injury was confirmed.

**Systematic review and meta-analysis**

Including the current study, a total of 7 studies were included in the review (Table 4) [8–13]. Six studies were included in quantitative analysis. All studies were retrospective in design and included only hospitalized COVID-19 patients within the U.S. The study by Pachtman et al. [13] was excluded as it included only pregnant patients. The quantitative analysis included data from 8 states or 55 hospitals. 12,577 patients were included in the quantitative analysis. The prevalence of myocardial injury ranged from 9.2 to 51%. The overall mean prevalence of myocardial injury was 27.2%. All studies included hospitalized patients.

In the meta-analysis, we found the presence of myocardial injury was significantly associated with mortality (HR 2.43, CI 2.28–3.6, \(P = 0.0005\), Fig. 1). Each study found an increased risk of mortality with myocardial injury.

**Discussion**

This study and review show myocardial injury is common (9–52%) in hospitalized COVID-19 patients in the U.S. [9–14]. This is in contrast to studies from China, which show relatively lower (7–28%) rates of myocardial injury in hospitalized COVID-19 patients [15–18]. We also found that development of myocardial injury in COVID-19 U.S. patients is associated with increased mortality, change of code status to “do not resuscitate”, discharge to skilled nursing facilities instead of home, development of acute kidney injury, circulatory shock, and arrhythmias.

We have, for the first time, shown in a meta-analysis on studies performed in the U.S. that myocardial injury significantly increases the mortality among hospitalized COVID-19 patients. This provides a high level of evidence. Similar to our results, a report of 416 patients from Wuhan, China demonstrated an HR of 3.41 (95% CI 1.62–7.16) for death in patients with myocardial injury compared with patients without myocardial injury [15]. Of note, Nuzzi V et al. found that in-hospital troponin elevation in Caucasian patients without myocardial injury at admission has a strong correlation with mortality [19]. We recommend that all patients admitted with COVID-19 should have troponin levels checked during their hospitalization. This, along with other clinical and laboratory variables, can provide further guidance on management and prognosis. The association of troponin elevation with increased mortality likely has two
main reasons. Firstly, troponin elevation in COVID-19 is more likely to occur in patients with underlying cardiac and non-cardiac comorbidities, placing them at an increased risk of poor outcomes. Secondly, cardiac injury in the setting of COVID-19 is a marker of tissue hypoxia, myocardial cytotoxicity, systemic cytokine upregulation, demand–supply mismatch, thrombosis, and plaque vulnerability [20–22]. All of these processes suggest advanced disease and poor prognosis.

The underlying factors that predispose to the development of myocardial injury are age, hypertension, underlying CVDs, and chronic kidney disease. The CVDs associated with the development of myocardial injury are ischemic heart disease, heart failure (both preserved and reduced EF), and atrial fibrillation. Our review of other U.S. studies suggests similar risk factors for developing myocardial injury [9–14].

### Table 3

Univariate and multivariate analysis for factors associated with myocardial injury

| Clinical factors                     | Univariate analysis | Multivariate analysis |
|--------------------------------------|---------------------|-----------------------|
|                                      | Odds ratio  | 95% confidence interval | P value | Odds ratio  | 95% confidence interval | P value |
| Age (years)                          | 1.06       | 1.04–1.08               | <0.001 | 1.05       | 1.02–1.1                | 0.00    |
| Sex                                  | 1.01       | 0.56–1.80               | 0.981  | –          | –                      | –       |
| Hypertension                         | 3.06       | 1.37–6.81               | 0.006  | 1.37       | 0.56–3.36              | 0.48    |
| Diabetes mellitus                    | 1.33       | 0.73–2.40               | 0.354  | –          | –                      | –       |
| Cardiovascular disease               | 4.12       | 2.24–7.56               | <0.001 | 2.0        | 1.1–4.0                | 0.04    |
| Ischemic heart disease               | 2.82       | 1.46–5.44               | 0.002  | –          | –                      | –       |
| HFrEF                                | 4.67       | 1.50–14.49              | 0.008  | –          | –                      | –       |
| HFrEF                                | 3.04       | 1.31–7.05               | 0.009  | –          | –                      | –       |
| Atrial fibrillation                  | 3.39       | 1.49–7.73               | 0.004  | –          | –                      | –       |
| ESRD on HD                           | 7.07       | 1.99–25.07              | 0.002  | 6.62       | 1.7–25                 | 0.06    |

**Hospital course and clinical outcome**

| EKG findings                         | Univariate analysis | Multivariate analysis |
|--------------------------------------|---------------------|-----------------------|
|                                      | Odds ratio  | 95% confidence interval | P value | Odds ratio  | 95% confidence interval | P value |
| Arrhythmia                           | 5.46       | 2.47–12.07              | <0.001 | 3.04       | 1.1–9.3                | 0.04    |
| Atrial fibrillation                  | 3.53       | 1.49–8.37               | 0.004  | –          | –                      | –       |
| 1st degree heartblock                | 1.84       | 0.33–10.30              | 0.488  | –          | –                      | –       |
| New BBB                              | 0.75       | 0.24–2.28               | 0.606  | –          | –                      | –       |
| ST depression or T wave inversion    | 2.34       | 1.09–4.97               | 0.027  | –          | –                      | –       |
| QT prolongation                      | 2.08       | 1.11–3.90               | 0.022  | –          | –                      | –       |
| Abnormal EKG                         | 3.47       | 1.90–6.34               | <0.001 | –          | –                      | –       |
| Abnormal BNP                         | 4.95       | 2.27–10.82              | <0.001 | 3.03       | 1.3–7.2                | 0.01    |
| High d-dimer                         | 2.40       | 1.11–5.20               | 0.026  | 1.2        | 0.4–3.5                | 0.73    |
| Acute kidney injury                  | 6.54       | 3.39–12.62              | <0.001 | 4.5        | 1.8–11                 | 0.001   |
| Invasive ventilation                 | 1.35       | 0.66–2.75               | 0.408  | –          | –                      | –       |
| Shock of any type                    | 3.70       | 1.85–7.39               | <0.001 | –          | –                      | –       |
| ARDS                                 | 1.44       | 0.67–3.08               | 0.354  | –          | –                      | –       |
| Ischemic stroke                      | 3.73       | 0.23–60.61              | 0.354  | –          | –                      | –       |
| Length of stay                       | 0.99       | 0.96–1.03               | 0.865  | –          | –                      | –       |
| Do not resuscitate and Comfort care  | 4.66       | 2.49–8.71               | <0.001 | –          | –                      | –       |
| Discharge to skilled Nursing facility| 2.94       | 1.41–6.10               | 0.004  | –          | –                      | –       |
| Death                                | 4.25       | 2.09–8.61               | <0.001 | –          | –                      | –       |

**In hospital medications**

| Hydroxychloroquine                   | 0.73       | 0.39–1.36               | 0.316  | –          | –                      | –       |
| Anticoagulation                      | 1.76       | 1.01–3.06               | 0.046  | –          | –                      | –       |
| ACEi/ARNi                            | 0.47       | 0.18–1.27               | 0.14   | –          | –                      | –       |
| Steroids                             | 3.73       | 1.84–7.57               | <0.001 | –          | –                      | –       |

HFrEF: congestive heart failure with preserved ejection fraction; HFrEF: congestive heart failure with reduced ejection; ARNI: angiotensin receptor-neprilysin inhibitor; ESRD: end stage renal disease on hemodialysis; BBB: bundle branch block (complete left or right). OR for continuous variables is calculated for 1-unit increments.
| References, study design | State, health system, number of hospitals | Total number of patients | Myocardial Injury N (%) | No myocardial injury N (%) | Troponin assay used | Patient population | Main finding |
|--------------------------|------------------------------------------|-------------------------|-------------------------|---------------------------|---------------------|--------------------|--------------|
| Lala et al. [10], Retrospective | New York, Mount Sinai Health System, 5 | 2736 | 985 (36) | 1751 (64) | Cardiac troponin I (Abbott Architect) | Hospitalized | COVID-19 patients with CVD were more likely to have myocardial injury than patients without CVD. Troponin elevation among patients hospitalized with COVID-19 was associated with higher risk of mortality |
| Majure et al. [11] Retrospective | New York, Northwell Health System 13 | 6247 | 1821 (29) | 4426 (71) | cardiac troponin I (Siemens Dimension Vista; Siemens Dimension EXL Systems); cardiac troponin T (Roche Troponin T STAT, 4th generation; Elecsys Troponin T Gen 5 STAT) | Hospitalized | Patients hospitalized with COVID-19 and elevated troponin had increased mortality compared with patients with normal troponin levels, which was independent of cardiovascular co-morbidities and elevated inflammatory markers |
| Case et al. [12] Retrospective | Maryland ( & Washington D.C.) MedStar Health System 11 | 2716 | 250 (9.2) | 2466 (90.8) | Troponin I | Hospitalized | COVID-19 patients with troponin elevation were at higher risk for mechanical ventilation and in-hospital mortality |
| De Michieli et al. [13] Retrospective | Minnesota, Wisconsin, Florida, Arizona Mayo Clinic Health System 17 | 367 | 169 (46) | 198 (54) | Hs-cardiac troponin T (Elecsys Troponin T Gen 5 STAT) | Hospitalized | Myocardial injury is prognostic in COVID-19 patients with regard to short-term mortality and major adverse events. A single hs-cTnT < 6 ng/L at presentation was associated with a more favorable prognosis |
| Pachtman Shetty et al. [14] Retrospective | New York Northwell Health 7 | 18 | 4 (22) | 14 (78) | Hs-Trop, Troponin T, Troponin I | Pregnant and immediately postpartum hospitalized for COVID-19 | Among pregnant women hospitalized for COVID-19, 20% were found to have elevations in troponin and 30% had elevated BNP |
| References, study design | State, health system, number of hospitals | Total number of patients | Myocardial Injury N (%) | No myocardial injury N (%) | Troponin assay used | Patient population | Main finding |
|--------------------------|------------------------------------------|-------------------------|-------------------------|---------------------------|---------------------|-------------------|--------------|
| Metkus et al. [9] Retrospective | Maryland, Johns Hopkins Health System 5 | 243                     | 124 (51)                | 119 (49)                  | Troponin T or Troponin I | COVID-19 patients who required intubation | Myocardial injury in patients with severe COVID-19 was a function of comorbidities, age, and multisystem organ dysfunction. Myocardial injury was associated with > two fold hazard for death. |
| Changal (2021) Retrospective* | Ohio, Promedica Health System 2 | 258                     | 58 (22.5)               | 210 (77.5)                | Troponin I (Sunquest) | Hospitalized COVID-19 patients | Myocardial injury was common, and predicted mortality, poor outcomes, and discharge to skilled nursing facility. |

*Our study as detailed in this manuscript

CVD cardiovascular disease, hs-cTnT high sensitivity cardiac troponin-t, BNP brain natriuretic peptide
While some studies performed outside of the U.S. have investigated the association of myocardial injury with COVID-19, such studies have often used non-guideline definitions that utilize imaging and electrocardiographic abnormalities for establishing diagnosis. This increases the margin of error in diagnosing the patients with true myocardial injury, making such studies less reliable. We utilized a uniform and validated definition for Type 2 MI in an attempt to avoid this error.

Although the patients with myocardial injury had poor outcomes, there was no significant difference in the healthcare costs. This is because many patients in the myocardial injury group were discharged to skilled nursing facilities rather than home, and likely would result in a higher overall cost. No other study in the review has studied the healthcare costs outcome.

There are some limitations to our study. All findings are retrospective in design and are thus limited by this. Another limitation is that only patients who had troponin levels checked during their hospitalization were included. However, only a small number of patients were excluded for lack of serum troponin testing (n = 11). All of the studies included patients prior to when vaccination against COVID-19 was available. Additionally, none of the included studies have provided data on coronary angiography in the included patients. Nevertheless, on this final point, diagnosis of myocardial injury is based on clinical, EKG, laboratory, and imaging data and coronary angiography is often not required to make this diagnosis. While some authors [23] have suggested a racial predisposition to adverse outcomes from COVID-19, the present study could not study the effect of race on mortality outcomes due to sample size limitations. Such data was also not available for meta-analysis.

To conclude, myocardial injury is a common phenomenon in hospitalized COVID-19 patients in the U.S. Elevated troponin in this population predicts a poor outcome and higher risk of mortality.

Abbreviations
ACEi: ACE inhibitor; ARBs: Angiotensin II receptor blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; BBB: Bundle branch block (complete left or right); BNP: Brain natriuretic peptide; CVD: Cardiovascular disease; CVVHD: Continuous venovenous hemodialysis; ESRD: End stage renal disease; HD: Hemodialysis; HFpEF: Heart failure with preserved ejection fraction; HFrEF: Heart failure with reduced ejection fraction; hs-cTnT: High sensitivity cardiac troponin-t; LOS: Length of stay; SNF: Skilled nursing facility; SPSS: Statistical package for the social sciences; U.S.: United States; VT: Ventricular tachycardia.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12872-021-02450-3.

Additional file 1. Search strategy and PRISMA checklist for the Meta-analysis.

Acknowledgements
None.

Authors’ contributions
KC: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Writing—original draft; Writing—review and editing. SV, SM, DP, MP: Data collection, data review, Writing—review and editing. SAS, TM: Data curation; Writing—review and editing. MS, MD and PKR: Conceptualization; Project administration; Resources; Writing—review and editing; Senior Authors. All authors have read and approved the manuscript.

Funding
None.

Availability of data and materials
Will be provided upon reasonable request. Please email Mujeeb A. Sheikh MD (smujeeb73@gmail.com) for requests.
Declarations

Ethics approval and consent to participate
Institutional Review Board of Promedica Health System in Toledo, Ohio, USA approved the study. Individual consents from patients were not required as institutional registry was used, and data was de-identified. The study protocol was carried out in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declared that they have no competing interest.

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Received: 19 August 2021 Accepted: 28 December 2021
Published online: 31 December 2021

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