

A Systematic Review of COVID-19 and Myocarditis

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Received May 19, 2020; Revised May 29, 2020; Accepted June 05, 2020

Abstract Background. The COVID-19 infection which emerged in December 2019, is caused by the virus SARS-CoV-2. Infection with this virus can lead to severe respiratory illness, however, myocarditis has also been reported. The purpose of this study is to identify the clinical features of myocarditis in COVID-19 patients. **Methods.** A systematic review was conducted to investigate characteristics of myocarditis in patients infected with COVID-19 using the search term “Coronavirus” or “COVID” and “myocarditis,” “heart,” or “retrospective.” Case reports and retrospective studies were gathered by searching Medline/Pubmed, Google Scholar, CINAHL, Cochrane CENTRAL, and Web of Science databases. 11 articles were selected for review. **Results.** COVID-19 myocarditis affected patients over the age of 50 and incidences among both genders were equally reported. Patients presented with dyspnea, cough, fever with hypotension and chest pain. Laboratory tests revealed leukocytosis with increased C-reactive protein, while arterial blood gas analysis demonstrated respiratory acidosis. All cardiac markers were elevated. Radiographic imaging of the chest showed bilateral ground glass opacities or bilateral infiltrates, while cardiac magnetic resonance imaging produced late gadolinium enhancements. Electrocardiography demonstrated ST-segment elevation or inverted T waves, while echocardiography revealed reduced left ventricular ejection fraction with cardiomegaly or increased wall thickness. Management with corticosteroids was favored in most cases, followed by antiviral medication. The majority of studies reported either recovery or no further clinical deterioration. **Conclusion.** Current available data on COVID-19 myocarditis is limited. Further research is needed to advance our understanding of COVID-19 myocarditis.

Keywords: COVID-19, SARS-CoV-2, Myocarditis, echocardiogram, cardiac MRI, electrocardiography

Cite This Article: Pramod Theetha Kariyanna, Bayu Sutarjono, Ekjot Grewal, Kamal Preet Singh, Lyudmila Aurora, Leanna Smith, Harshith Priyan Chandrakumar, Apoorva Jayarangaiah, Sarah A. Goldman, Moro O. Salifu, and Isabel M. McFarlane, “A Systematic Review of COVID-19 and Myocarditis.” *American Journal of Medical Case Reports*, vol. 8, no. 9 (2020): 299-305. doi: 10.12691/ajmcr-8-9-11.

1. Introduction

A newly identified viral illness emerged in late December 2019 that has subsequently spread rapidly throughout the world [1]. A new coronavirus, later named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the pathogen that caused severe respiratory illness also known as coronavirus disease 2019 or COVID-19 [2].

SARS-CoV-2 binds with high affinity to human angiotensin-converting enzyme 2 receptor (ACE 2) [3]. ACE-2 is widely expressed throughout the body, including in the lungs and the heart [4]. Although scarce, serious systemic infections such as myocarditis have been reported in connection with COVID-19.

Myocarditis, an inflammatory condition affecting the myocardium, results from a wide spectrum of both infectious and non-infectious causes. Many different viruses have been implicated, including the Middle East Respiratory Syndrome (MERS) coronavirus [5], which closely resembles SARS-CoV-2. Myocarditis is suspected on the basis of elevated troponins in the patient’s blood, cardiac arrhythmias or diffuse ST elevation on electrocardiogram (ECG) and left ventricular wall motion abnormalities (regional or global hypokinesia) on echocardiogram. The clinical presentations of myocarditis include subclinical, subacute, acute and fulminant forms, and abrupt-onset myocarditis is known to be associated with significant severity [6].

The annual incidence of acute myocarditis from all causes is approximately 22 cases per 100,000 population, with heart failure occurring in 0.5% to 4.0% of these cases [7]. Myocarditis can occur in 1% to 5% of all patients with

acute viral infections [8]. To date, clinical data on myocarditis caused by SARS-CoV-2 is scarce. Patient characteristics, clinical course, degree of severity, imaging and electrocardiographic features, management and outcomes of myocarditis are just some of relevant data clinicians should have access to when treating patients with COVID-19 myocarditis. Therefore, we conducted a systematic review of myocarditis in COVID-19 patients to evaluate clinical features, diagnostic tests and current therapeutic management.

2. Methods

2.1. Protocol and Registration

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was adhered to for this systematic review [9]. The protocol was not registered.

2.2. Eligibility Criteria

2.2.1. Inclusion Criteria

Only articles that reported myocardial inflammation or myocarditis in association with COVID-19 were included.

2.2.2. Exclusion Criteria

Studies were excluded if: 1) Articles were not case reports, case series or observational studies, or 2) Articles

were reviews or editorials. The language the article was written in was not a limitation.

2.3. Information Sources and Search Strategies

A comprehensive literature search was completed using Medline/Pubmed, Google Scholar, CINAHL, Cochrane CENTRAL and Web of Science databases up to and including 29 April 2020, using the terms “Coronavirus” or “COVID” and “myocarditis,” “heart” or “retrospective.”

2.4. Study Selection

Articles were triaged based on whether titles or abstracts met the inclusion criteria. Full-text articles were then read, and those that did not satisfy the inclusion criteria or fit exclusion criteria were excluded. A summary of study characteristics is included in Table 1.

2.5. Data Collection Process and Data Items

Data extracted from articles included the name of first author, year and country of publication and study design. Patient variables including age, sex and presenting complaints on admission were sought from all studies. Laboratory tests and diagnostic studies, as well as myocarditis management strategies and patient outcomes, including complications, were obtained from case studies.

Table 1. Summary Assessment of the Risk of Bias for the Included Studies

| Reference, publication year | Were the patient's demographic characteristics clearly described? | Was the patient's history clearly described and presented as a timeline? | Was the patient's clinical condition on presentation clearly described? | Were diagnostic tests or assessment methods and results clearly described? | Was the intervention or treatment procedure(s) clearly described? | Was the post-intervention clinical condition clearly described? | Were adverse events (harms) or unanticipated events identified and described? | Does the case report provide takeaway lessons? | Total score |
|---------------------------------|---|--|---|--|---|---|---|--|-------------|
| Deng et al., 2020 [10] | ✓ | Medical hx unknown | ✓ | All laboratory tests not included | No | No | No | ✓ | 37.50% |
| Doyen et al., 2020 [13] | ✓ | ✓ | ✓ | All laboratory tests not included | ✓ | ✓ | ✓ | ✓ | 87.50% |
| Hu et al., 2020 [14] | ✓ | Medical hx unknown | ✓ | All laboratory tests not included | ✓ | ✓ | ✓ | ✓ | 75% |
| Inciardi et al., 2020 [15] | ✓ | ✓ | ✓ | ✓ | ✓ | Outcome unknown | ✓ | ✓ | 87.50% |
| Irabien-Ortiz et al., 2020 [16] | ✓ | ✓ | ✓ | All laboratory tests not included | ✓ | Outcome unknown | ✓ | No | 62.50% |
| Kim et al., 2020 [17] | ✓ | Medical hx unknown | ✓ | All laboratory tests not included | No | No | No | No | 25% |
| Paul et al., 2020 [18] | ✓ | ✓ | ✓ | All laboratory tests not included | ✓ | ✓ | ✓ | No | 75% |
| Ruan et al., 2020 [11] | No | No | No | ✓ | ✓ | No | No | ✓ | 37.50% |
| Sala et al., 2020 [19] | ✓ | ✓ | ✓ | All laboratory tests not included | ✓ | ✓ | ✓ | No | 75% |
| Tavazzi et al., 2020 [20] | Sex missing | ✓ | ✓ | All laboratory tests not included | ✓ | ✓ | ✓ | ✓ | 75% |
| Zeng et al., 2020 [21] | ✓ | ✓ | Admission vitals missing | All laboratory tests not included | Dosage missing | ✓ | ✓ | ✓ | 63% |

2.6. Synthesis of Results and Summary of Measures

Information was assessed if it was reported by two or more articles. Data were tabulated, evaluated and summarized. From the retrospective studies, for Deng et al. [10] the diagnosis of myocarditis was assumed, while Ruan et al. [11] gathered patient profiles and presenting symptoms from the deceased population.

2.7. Risk of Bias of the Included Studies

Potential biases of the included studies were analyzed utilizing the study characteristics. Two independent reviewers evaluated the methodological quality of the eligible studies. A third reviewer evaluated papers for which no decision regarding bias could be reached. The Joanna Briggs Institute critical appraisal tool for case reports was selected for use in this systematic review [12]. The presence of a bias was determined for each article using a checklist the eight questions included in Table 1. The articles received scores to indicate their degree of biases; low (included), high (excluded) or uncertain (more information is required). For the purpose of this study, if “yes” was answered for half or more of the eight questions on the checklist, the study was considered to be at low risk

of bias. Similarly, an answer of “no” to half or more of the eight questions meant the study was determined to be at high risk of bias. Whereas “unclear” answers were equal to or greater than 50% response.

3. Results

3.1. Study Selection

Five databases were used to find the 1076 articles related to COVID-19 and myocarditis. Eleven studies were then deemed eligible for inclusion in this review [10,11,13,14,15,16,17,18,19,20,21]. A PRISMA flow diagram detailing the process of identification, inclusion and exclusion of studies is shown in Figure 1.

3.2. Study Characteristics

Of the 11 included articles, nine were case reports [13,14,15,16,17,18,19,20,21] and two were retrospective studies [10,11]. All but one [21] were peer-reviewed. All articles were published in 2020. Five studies were conducted in Asia [10,11,14,17,21] and six were conducted in Europe [13,15,16,18,19,20]. China produced the most articles [10,11,14,21] followed by Italy [15,19,20].

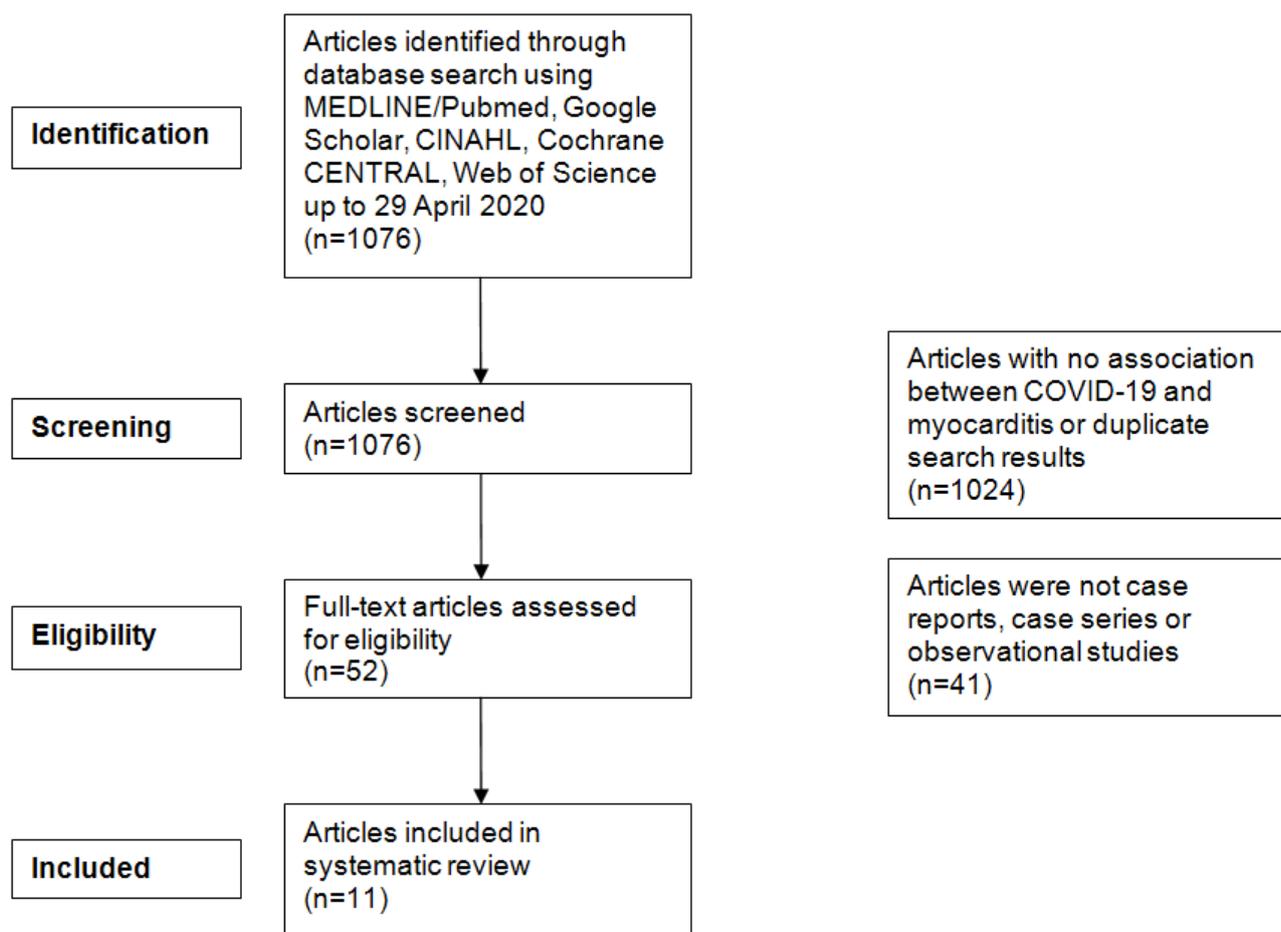


Figure 1. Flow diagram of literature search and selection criteria adapted from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Table 2. Summary of Included Articles

| Reference number & publication year | Country | Type of study | Patient profile (age in years, sex) | Diagnosis |
|-------------------------------------|-------------|------------------------------------|-------------------------------------|---|
| Deng et al., 2020 [10] | China | Retrospective study, single center | 74, male | Possible myocarditis |
| Doyen et al., 2020 [13] | France | Case report | 69, male | Acute myocarditis |
| Hu et al., 2020 [14] | China | Case report | 37, male | Fulminant myocarditis |
| Inciardi et al., 2020 [15] | Italy | Case report | 53, female | Acute myopericarditis |
| Irabien-Ortiz et al., 2020 [16] | Spain | Case report | 59, female | Fulminant myocarditis |
| Kim et al., 2020 [17] | South Korea | Case report | 21, female | Acute myocarditis |
| Paul et al., 2020 [18] | France | Case report | 35, male | Acute myocarditis |
| Ruan et al., 2020 [11] | China | Retrospective study, multi-center | Unknown | Possible fulminant myocarditis |
| Sala et al., 2020 [19] | Italy | Case report | 43, female | Acute virus-negative lymphocytic myocarditis |
| Tavazzi et al., 2020 [20] | Italy | Case report | 69, female | Myocardial localization of virus in cardiogenic shock |
| Zeng et al., 2020 [21] | China | Case report, non-peer reviewed | 63, male | Fulminant myocarditis |

3.3. Risk of Bias within the Studies

In comparison of the case reports, the majority of articles were determined to have low risk of bias [13,14,15,16,18,19,20,21]. Only one study was identified as having high risk of bias [17]. Both retrospective studies were rated as having high risk of bias [10,11]. These results are included in Table 1.

3.4. Results of Individual Studies

Nine case reports were selected for the systematic review. In the French study by Doyen et al. [13], the authors described a 69-year-old Italian man who tested positive for COVID-19, developed elevated troponins and ECG changes and was managed with hydrocortisone. Hu et al. [14] reported a case of a 37-year-old COVID-19 male from China with fulminant myocarditis who was treated with glucocorticoids and intravenous human immunoglobulin. Inciardi et al. [15] reported a 53-year-old Italian woman with COVID-19 with acute myopericarditis with evidence of systolic dysfunction on echocardiogram. In the only article not written in English, Irabien-Ortiz et al. [16] described a 59-year-old woman from Spain with COVID-19 and fulminant myocarditis in the absence of initial respiratory symptoms. In the study by Kim et al. [17], a 21-year-old woman from South Korea presented with COVID-19 and myocarditis. In the French study by Paul et al. [18], the authors reported a 35-year-old male positive for COVID-19 with acute myocarditis without fever, cough or pulmonary involvement. The article by Sala et al. [19] described a 43-year-old Italian woman diagnosed with COVID-19 and acute virus-negative lymphocytic myocarditis. Tavazzi et al. [20] described a case of a 69-year-old Italian woman with COVID-19 and low-grade myocardial inflammation; viral particles were seen in the patient's myocardium and she required venous-arterial extracorporeal membrane oxygenation. Finally, Zeng et al. [21] reported a 63-year-old Chinese man with COVID-19 complicated by fulminant myocarditis.

Two retrospective studies were selected for the systematic review. In the first study, Deng et al. [10] described 14 of the original 112 patients hospitalized with COVID-19 in a major tertiary teaching hospital in China, who presented with cardiac abnormalities similar to myocarditis. In the second retrospective study Ruan et al.

[11] reported that some of the 150 COVID-19 positive patients from two hospitals in China died of fulminant myocarditis. A summary of findings from all studies is presented in Table 2.

3.5. Synthesis of Results

3.5.1. Patient Profiles

Among the nine case reports, COVID-19 patients with myocarditis were 51.8 ± 16.9 years of age, and males and females were equally affected [13,14,15,16,17,19,20,21]. In contrast, the retrospective studies described the typical myocarditis patient as male and older than 55 years of age [10,11]. The youngest patient described with COVID-19-related myocarditis was a 21-year old woman [17].

3.5.2. Presenting Complaints

The predominant complaint on presentation was dyspnea [10,11,13,14,16,17,19,20,21], followed by coughing [10,11,15,17,20,21], fever [10,11,13,14,15,17,21], and chest pain [10,13,16,19,21]. The mean temperature recorded was $37.53 \pm 1.3^\circ\text{C}$ [10,15,19,20,21], and the mean blood pressure was $85/58.3 \pm 22.4/14.6$ [10,14,15,16,19,20]. The distribution of presenting complaints and associated symptoms is found in Table 3.

Table 3. Most common clinical manifestations among patients with COVID-19 and myocarditis on admission as reported from all articles

| Symptom | % |
|------------|-----------------------------------|
| Dyspnea | 81.8 [10,11,13,14,16,17,19,20,21] |
| Fever | 54.6 [10,11,13,15,17,21] |
| Cough | 54.6 [10,11,15,17,20,21] |
| Chest pain | 54.6 [10,14,16,18,19,21] |

3.5.3. Past Medical History

There were insufficient data regarding past medical history.

3.5.4. Laboratory Tests

A summary of laboratory tests is found in Table 4. Mean white blood cell (WBC) count was elevated at $17,383 \pm 4,947$ cells/mm³ [16,20], and C-reactive protein (CRP) levels were increased at 31.2 ± 20.0 mg/L [13,15,19,20]. Arterial blood gas analyses showed

respiratory acidosis with a mean pH of 7.24 ± 0.17 [13,15,20,21] and mean pCO_2 of 51.2 ± 8.2 mmHg [13,15,21]. Average oxygen saturation was $94.6 \pm 4.1\%$ [13,15,16,19,21], with a pO_2 of 91.0 ± 37.2 mmHg [13,15,20,21]. All studies reported either increased troponin-I [13,17,20,21] or troponin-T [14,15,16,19], along with elevated creatinine kinase-myocardial band (CK-MB) [14,15,21] and brain natriuretic peptide (BNP) [14,15,16,17,19,20,21].

Table 4. Trends of laboratory values of COVID-19 patients with myocarditis

| | Trends | (Standard range) |
|--------------------------------|------------------------------------|------------------|
| Vitals | | |
| Temperature, Celsius | Elevated [13,15,19,20,21] | (<37.5) |
| Systolic blood pressure, mmHg | Decreased [14,15,16,19,20] | (90-120) |
| Diastolic blood pressure, mmHg | Decreased [14,15,16,19] | (60-80) |
| Arterial blood gas | | |
| pH | Low [13,15,20,21] | (7.35-7.45) |
| pCO_2 , mmHg | High [13,15,21] | (35-45) |
| pO_2 , mmHg | Normal [13,15,20,21] | (75-100) |
| SaO ₂ , % | Normal [13,15,16,19] | (>94) |
| Inflammatory markers | | |
| WBC, cells/mm ³ | Elevated [13,16,20] | (4,500-11,000) |
| CRP, mg/L | Elevated [15,19,20] | (<8.0) |
| Cardiac markers | | |
| Troponin-I, ng/mL | Elevated [13,17,18,20,21] | (<0.04) |
| Troponin-T, ng/mL | Elevated [14,15,16,19] | (<0.01) |
| CK-MB, ng/mL | Elevated [14,15,21] | (<5.0) |
| BNP, pg/mL | Elevated [14,15,16,17,19,20,21] | <125 |

3.5.5. Diagnostic Studies

A list of the diagnostic tests and imaging techniques utilized in the studies is provided in Table 5. All patients were confirmed COVID-19 positive. Bilateral infiltrates were discovered in 50% of chest radiographs [17,19,21] and bilateral ground glass opacities were seen in all patients who underwent chest computed tomography (CT) [13,14,17,19,20,21].

Table 5. Common findings on diagnostic tests of COVID-19 patients with myocarditis

| Tests | Proportion Recorded from Articles Reviewed |
|--|--|
| Imaging (X-ray, CT, MRI) | |
| Late gadolinium enhancement | 100 [13,15,17,18,19] |
| Bilateral infiltrates/ground glass opacities | 66.7 [13,14,17,19,20,21] |
| Cardiomegaly | 33.3 [14,15,17] |
| Echocardiography | |
| Decreased LVEF | 66.7 [14,15,17,19,20,21] |
| Cardiomegaly or wall thickness | 66.7 [13,14,15,16,20,21] |
| Pericardial effusion | 33.3 [14,15,16] |
| Electrocardiography | |
| ST-segment elevation | 55.6 [14,15,16,18,19] |
| T-wave inversion | 33.3 [13,15,20] |

Cardiac magnetic resonance imaging (MRI) revealed late gadolinium enhancement [13,15,17,18,19] in all of the patients, while myocardial edema was identified in more than half of the images [15,17,19]. Fifty percent of the imaging studies revealed cardiomegaly or vascular redistribution [14,16,17]. Coronary artery stenosis was not appreciated on the CT angiography studies [14,17,19].

Electrocardiograms revealed ST-segment elevation in five cases [14,15,16,18,19], and inverted T waves in three cases [13,15,20]. In six of the studies, 2-D echocardiography revealed decreased left ventricular ejection fraction (LVEF) [14,15,17,19,20,21], and in the same number of cases, cardiomegaly or increased wall thickness were observed [13,14,15,16,20,21]. Pericardial effusion was present in only three patients [14,15,16]. Two studies reported the results of endomyocardial biopsies [19,20]; both samples revealed active inflammation, and only one found viral particles within the myocardium [20].

3.5.6. Management of Myocarditis

Corticosteroids were utilized in attempted treatment in 75% of studies [13,14,15,16,20,21], while the use of the antiviral medications lopinavir-ritonavir was reported in 62.5% of studies [14,15,16,19,20,21]. The utilization of hydroxychloroquine [15,19,20], human immunoglobulin [14,16,21], piperacillin-tazobactam [14,20,21], and extracorporeal membrane oxygenation [16,20,21] each as single therapeutic interventions was described in 37.5% of case reports. The use of inotropes and/or vasopressors was reported in 50% of studies [14,15,16,20].

3.5.7. Outcome

Patient outcomes were included in the majority of the case reports [13,14,17,18,19,20,21]. Only one death was reported, and it was non-myocarditis-related [20]. The remaining articles reported either recovery [14,15,16,19,21] or no further impairment of LVEF [20].

3.6. Risk of Bias across the Studies

Due to the nature of the descriptive studies, the results presented are liable to investigator bias, selection procedure bias and selection bias.

3.6.1. Limitation of the Study

Statistical analyses were not performed as there were no control/comparison groups in the included studies.

4. Discussion

In order of prevalence, the clinical manifestations of the severe acute respiratory syndrome due to COVID-19 are fever, cough and fatigue [22]. Typically, myocarditis presents with fever, dyspnea and/or chest pain [23], which hampers the recognition and clinical diagnosis of myocarditis during the COVID-19 pandemic. We have identified through this systematic review that patients with COVID-19 myocarditis will commonly present with dyspnea, followed by coughing, fever and chest pain.

Serum biomarkers are conventionally used to confirm suspected acute myocarditis. While troponin was elevated

in a few patients with acute myocarditis [24], elevated serum cardiac troponins were almost always seen in fulminant myocarditis [6]. Heightened levels of troponins have been described in many patients infected with COVID-19, with particular differences observed between deceased and surviving patients [25]. The absence of increased serum cardiac troponins, however, does not rule out myocarditis [6]. Elevated CK-MB and BNP were often elevated in myocarditis and can provide insight into prognosis [26]. CRP was commonly elevated, although normal levels did not exclude myocarditis [27]. CRP has been shown to be above the normal range in most COVID-19 patients as well [22]. This systematic review revealed increases in troponins, CK-MB, BNP, and CRP in COVID-19 myocarditis.

ST-segment abnormalities on ECG were demonstrated in 71.4% of patients. The ECGs of most patients with myocarditis demonstrated non-specific features including sinus tachycardia, ST-wave and T-wave abnormalities, and occasional atrioventricular or bundle branch block [28]. While ST-segment elevations in contiguous leads in a segmental fashion or in a nonvascular distribution are common electrocardiographic signs of myocarditis, they can often be mistaken for coronary occlusion [6].

Echocardiographic patterns of dilated, hypertrophic, restrictive and ischemic cardiomyopathies, particularly increased sphericity and left ventricular volume, have been described in histologically proven myocarditis [29]. Impaired LVEF on presentation is an independent predictor of a fulminant disease course [30]. This systematic review found that the majority of COVID-19 myocarditis patients had cardiomegaly, pleural effusion and reduced LVEF.

Dilated ventricles are typical of acute myocarditis, although the fulminant form can lead to increased left ventricular wall thickness as a result of active inflammation [29]. The majority of the cases of COVID-19 myocarditis reviewed here displayed cardiomegaly. Furthermore, the development of pneumonia seen as ground glass opacities on chest CT, the characteristic feature of COVID-19, was found in all patients in this systematic review [22,31].

There are only a few prospective blinded randomized trials that have specifically targeted viral infections or the associated inflammatory cascades in myocarditis. Presently, evidence does not support the routine use of corticosteroids or intravenous immunoglobulin alone [32,33], although combined treatment of corticosteroids with immunosuppressants has shown non-significant increases in LVEF [32]. The use of extracorporeal membrane oxygenation, however, has been shown to provide favorable outcomes for patients with myocarditis and sepsis [34], as well as fulminant myocarditis [35].

Among COVID-19 patients, there is limited evidence of the effectiveness of current management and treatment strategies. A recently published systematic review concluded that treatment with corticosteroids, mainly methylprednisolone, in patients infected with a coronavirus like COVID-19, SARS, MERS, etc., is associated with higher mortality, longer hospitalization, and higher rates of bacterial infection and electrolyte abnormalities [36]. A combination treatment of steroids with immunomodulatory therapy and antibiotics was used

in a minority of studies. Extracorporeal membrane oxygenation was used in three studies with mixed results.

It is difficult to evaluate the effectiveness of the various treatment strategies currently being attempted in cases of COVID-19 given the lack of randomized control trial results to date. While current evidence shows no significant difference in the prognosis of virus-positive and virus-negative patients with myocarditis [37], that may change within the COVID-19 climate.

In conclusion, our systematic review provides a comprehensive characterization of clinical features among COVID-19 patients with myocarditis. Data are presently limited, therefore more research, particularly of the epidemiological type, is needed to improve our understanding of COVID-19 myocarditis.

Acknowledgements

This work is supported in part by Dr. Moro O. Salifu's efforts through NIH Grant # S21MD012474.

References

- [1] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020.
- [2] Joint Mission Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) 2020. Available from <https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf>
- [3] Letko M, Marzi A, Munster V. Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B beta-coronaviruses. *Nat Microbiol* 2020.
- [4] Hamming I, Timens W, Bultuis MLC, Lely AT, Navis GJ, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus: a first step in understanding SARS pathogenesis. *J Pathol* 2004; 203: 631-7.
- [5] Alhagbani T. Acute myocarditis associated with novel middle east respiratory syndrome coronavirus. *Ann Saudi Med* 2016; 36(1): 78-80.
- [6] Kociol RD, Cooper LT, Fang JC, Moslehi JJ, Pang PS, Sabe MA, Shah RV, Sims DB, Thiene G, Vardeny O, American Heart Association Heart Failure and Transplantation Committee of the Council on Clinical Cardiology. Recognition and initial management of fulminant myocarditis: a scientific statement from the American Heart Association. *Circulation* 2020; 141(6): e69-92.
- [7] Vos T, Barber RM, Bell B, Bertozzi-Billa A, Birkyukov S, Bolliger I, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden Disease Study 2013. *Lancet* 2015; 386: 743-800.
- [8] Kyto V, Saraste A, Voipio-Pulkki LM, Saukko P. Incidence of fatal myocarditis: a population-based study in Finland. *Am J Epidemiol* 2007; 165: 570-4.
- [9] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic review and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.
- [10] Deng Q, Hu B, Zhang Y, Wang H, Zhou X, Hu W, Cheng Y, Yan J, Ping H, Zhou Q. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. *Int J Cardiol* 2020.
- [11] Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* 2020..

- [12] Moola S, Munn Z, Tufanaru C, Aromataris E, Sears K, Sfetcu R, Currie M, Qureshi R, Mattis P, Lisy K, Mu P. Chapter 7: Systematic reviews of etiology and risk. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute Reviewer's Manual. The Joanna Briggs Institute 2017.
- [13] Doyen D, Morceri P, Ducreux D, Dellamonica J. Myocarditis in a patient with COVID-19: a cause of raised troponin and ECG changes. *Lancet* 2020.
- [14] Hu H, Ma F, Wei X, Fang Y. Coronavirus fulminant myocarditis treated with glucocorticoid and human immunoglobulin. *Eur J Heart* 2020.
- [15] Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, Cani DS, Cerini M, Farina D, Gavazzi E, Maroldi R, Adamo M, Ammirati E, Sinagra G, Lombardi CM, Metra M. Cardiac involvement in a patient with coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020.
- [16] Irabien-Ortiz A, Carreras-Mora J, Sionis A, Pamies J, Montiel J, Tauron M. Fulminant myocarditis due to COVID-19. *Rev Esp Cardiol* 2020.
- [17] Kim I, Kim JY, Kim HA, Han S. COVID-19-related myocarditis in a 21-year-old female patient. *Eur J Heart* 2020.
- [18] Paul J, Charles P, Richaud C, Caussin C, Diakov C. Myocarditis revealing COVID-19 infection in a young patient. *Eur Heart J Cardiovasc Imaging* 2020.
- [19] Sala S, Peretto G, Gramagna M, Palmisano A, Villatore A, Vignale D, De Cobelli F, Tresoldi M, Cappelletti AM, Basso C, Godino C, Esposito A. Acute myocarditis presenting as a reverse Tako-Tsubo syndrome in a patient with SARS-CoV-2 respiratory infection. *Eur J Heart* 2020.
- [20] Tavazzi G, Pellegrini C, Maurelli M, Belliato M, Sciutti F, Bottazzi A, Sepe PA, Resasco T, Camporotondo R, Bruno R, Baldanti F, Paolucci S, Pelenghi S, Iotti GA, Mojoli F, Arbustini E. Myocardial localization of coronavirus COVID-19 cardiogenic shock. *Eur J Heart Fail* 2020.
- [21] Zeng J, Liu Y, Yuan J, Wang F, Wu W, Li J, Wang L, Gao H, Wang Y, Dong C, Li Y, Xie X, Feng C, Liu L. First case of COVID-19 infection with fulminant myocarditis complication: case report and insights. *Preprints* 2020.
- [22] Fu L, Wang B, Yuan T, Chen X, Ao Y, Fitzpatrick T, Li P, Zhou Y, Lin Y, Duan Q, Luo G, Fan S, Lu Y, Feng A, Zhan Y, Liang B, Cai W, Zhang L, Du X, Li L, Shu Y, Zou H. Clinical characteristics of coronavirus disease 2019 (COVID-19) in China: a systematic review and meta-analysis. *J Infect* 2020; S0163-4453(20)30170-5.
- [23] Cooper Jr LT. Myocarditis. *N Engl J Med* 2009; 360(15): 1526-38.
- [24] Smith SC, Ladenson JH, Mason JW, Jaffe AS. Elevations of cardiac troponin I associated with myocarditis. Experimental and clinical correlates. *Circulation* 1997; 95: 163-6.
- [25] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, Wu Y, Zhang L, Y Z, Fang M, Yu T, Wang Y, Pan S, Zou X, Yuan S, Shang Y. Clinical course and outcomes of critically ill patients with SARS-CoV2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020.
- [26] Park JP, Song J-M, Kim S-H, et al. In-hospital prognostic factors in patients with acute myocarditis. *J Am Coll Cardiol* 2009; 53:A144-97(abstr 1042-178).
- [27] Caforio AL, Pankuweit S, Arbustini E, Basso C, Gimeno-Blanes J, Felix SB, Fu M, Heliö T, Heymans S, Jahns R, Klingel K, Linhart A, Maisch B, McKenna W, Mogensen J, Pinto YM, Ristic A, Schultheiss H, Swggewiss H, Tavazzi L, Thiene G, Yilmaz A, Charron P, Elliott P, European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Current state of knowledge on aetiology, diagnosis, management, and therapy of myocarditis: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2013; 34: 2636-48, 2648a.
- [28] Nakashima H, Katayama T, Ishizaki M, Takeno M, Honda Y, Yano K. Q wave and non-Q wave myocarditis with special reference to clinical significance. *Jpn Heart J* 1998; 39:763-74.
- [29] Sagar S, Liu PP, Cooper Jr LT. Myocarditis. *Lancet* 2012; 379: 738-47.
- [30] Caforio ALP, Calabrese F, Angelini A, Tona F, Vinci A, Bottaro S, Ramondo A, Carturan E, Iliceto S, Thiene G, Daliento L. A prospective study of biopsy-proven myocarditis: Prognostic relevance of clinical and aetiopathogenetic features at diagnosis. *Eur Heart J* 2007; 28: 1326-33.
- [31] Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, Liu L, Shan H, Lei C, Hui DSC, Du B, Li L, Zeng g, Yuen K, Chen R, Tang C, Wang T, Chen P, /Xiang J, Li S, Wang J, Liang Z, Peng Y, Wei L, Liu Y, Hu Y, Peng P, Wang J, Liu J, Chen Z, Li G, Zheng Z, Qiu S, Luo J, Ye C, Zhu S, Zhong N, China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; NEJMoa2002032.
- [32] Winter M, Sulzgruber P, Koller L, Bartko P, Goliash G, Niessner A. Immunomodulatory treatment for lymphocytic myocarditis - a systematic review and meta-analysis. *Heart Fail Rev* 2018; 23(4): 573-81.
- [33] Yen C, Hung M, Wong Y, Chang C, Lai C, Wu K. Role of intravenous immunoglobulin therapy in the survival rate of pediatric patients with acute myocarditis: a systematic review and meta-analysis. *Sci Rep* 2019; 9(1): 10459.
- [34] Sangli SS, Noronha SF, Mourad B, Jean R, Bohman JK, Seelhammer TG. A systematic review of preexisting sepsis and extracorporeal membrane oxygenation. *ASAIO J* 2020; 66(1): 1-7.
- [35] Hekimian G, Jovanovic T, Brechot N, Lebreton G, Leprince P, Trouillet J, Schmidt M, Nieszkowska A, Besset S, Chastre J, Combes A, Luyt C. When the heart gets the flu: fulminant influenza B myocarditis: a case-series report and review of the literature. *J Crit Care* 2018; 47: 61-5.
- [36] Yang Z, Liu J, Zhou Y, Zhao X, Zhao Q, Liu J. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. *J Infect* 2020; S0163-4453(20)30191-2.
- [37] Chen W, Guo Y, Zhang D, Zhang H. Long-term prognosis of suspected myocarditis and cardiomyopathy associated with viral infection of the myocardial tissue: a meta-analysis of cohort studies. *Cardiovasc Ther* 2019; 2019: 9342792.

