Corticosteroid Therapy in Management of Myocarditis Associated with COVID-19; a Systematic Review of Current Evidence

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Abstract: Introduction: Myocarditis in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) seems to be associated with a higher mortality rate. This study aims to summarize the latest evidence on whether the use of corticosteroids in patients with myocarditis associated with COVID-19 is necessary. Methods: We performed an extensive search using a combination of search terms in PubMed, Europe PMC, ProQuest, EBSCOhost, and Google Scholar up to January 2021. Full-text articles that met the predefined inclusion criteria were included in the present study. Results: The full-texts of 18 articles have been reviewed. Thirteen out of the eighteen (72%) patients who got corticosteroid administration experienced major clinical improvements during follow-up while the other five (28%) were experiencing uneventful events. The mean age of the reported patients was 47.8±13.2 years. There was no gender predominance. Most of the reported cases were from USA (39%) followed by Spain, China, and UK (11% each), while Brazil, Colombia, France, Belgium, and Italy contributed one case each. Various corticosteroids were used but the most commonly applied were methylprednisolone (89%), hydrocortisone (5.5%), and prednisolone (5.5%). The most common route of administration among the studies was intravenous administration and the duration of treatment varied between one and fourteen days. Conclusion: A review of the currently available literature shows that with the use of corticosteroid agents in treating myocarditis associated with COVID-19, favorable outcomes are attainable. Well-established randomized clinical trials are needed to evaluate the efficacy and safety of using corticosteroids in this condition.

Keywords: COVID-19; myocarditis; corticosteroid; treatment

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1. Introduction

Late in 2019, the world was staggered by the emergence of a new virus derived from Wuhan, China, which caused severe pneumonia and was later called the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease caused by the virus was named coronavirus disease 19 (COVID-19) (1). This disease has led to more than 20 million active cases in 218 countries with more than 1.5 million people losing their lives (2). In the midst of this pandemic, a lot is still yet to be discovered, including the true magnitude of the disease.

It was later discovered that since it binds with angiotensin converting enzyme (ACE) 2 receptors, which are also present in endothelial cells, it also affects the cardiovascular system and could manifest as myocarditis (3, 4). As many studies investigating the mechanism of multiple organ dysfunction syndrome (MODS) associated with COVID-19 indicated, systemic hyper inflammation syndrome has become a leading theory to explain the condition (5). Currently, there is no guideline that specifically addresses use of corticosteroids in treatment of myocarditis caused by COVID-19. Considering that uncertainty remains regarding this issue, we aimed to systematically review the use of corticosteroids in patients with myocarditis associated with COVID-19. Considering that uncertainty remains regarding this issue, we aimed to systematically review the use of corticosteroids in patients with myocarditis associated with COVID-19. We hypothesized that the addition of immunosuppressant therapy e.g. corticosteroids at this stage may reduce the severity of this hyperinflammatory condition.
2. Methods

2.1. Protocol and Registration

This systematic review was conducted in line with the Cochrane Handbook for Systematic Reviews of Interventions and reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (6, 7). The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO), under registration number CRD42020223524.

2.2. Search Strategy

Due to the lack of research articles, we performed a comprehensive search on case reports/series that presents patients with myocarditis associated with COVID-19 who were treated with corticosteroids using keywords ((COVID 19) OR (COVID-19) OR (Coronavirus) OR (Coronavirus disease) OR (Novel Coronavirus) OR (Novel human coronavirus) OR (SARS coronavirus) OR (SARS-CoV) OR (SARS-CoV-2) OR (SARS-CoV2) OR (SARS-CoV-2) OR (2019-nCoV)) AND ((Myocarditis) OR (Carditis) OR (Pericarditis) OR (Myopericarditis)) AND (Corticosteroid)) from the time in which SARS-CoV-2 was identified (January 2020) up until January 2021 through PubMed, EuropePMC, ProQuest, EBSCOhost, and Google Scholar. To ensure the identification of all relevant articles and publications, hand-searched articles from reference lists were also reviewed as an additional source of studies. We did not include words related to the outcomes of interest in order to obtain the largest number of search results possible. Our search was in line with PRISMA guidelines and the flowchart in Figure 1 portrays the search and screening processes.

2.3. Eligibility Criteria

In the present study, all cases using corticosteroids for patients with myocarditis associated with COVID-19 were included to be reviewed. Exclusion criteria comprised animal studies, expert opinions, literature review studies, news articles, letters, editorials, guidelines, and any studies that did not mention the outcomes and specify the corticosteroid used in the study. We also limited our search to articles written in English. The outcomes of interest were all-cause mortality, clinical improvement, and hospital discharge.

2.4. Study Selection and Data Collection Process

Articles were sorted based on whether titles or abstracts met the inclusion criteria. Full-text articles were then read, and any duplicate studies were deleted, and those that did not satisfy the inclusion criteria were excluded. Data from the article were extracted and summarized based on predesigned tables that consisted of name of the first author, year of publication, country in which the study was conducted, age and sex distribution of the patients, complete assessment of the patient, corticosteroid used, dose, route, and duration of administration, other medications, and outcomes. All steps of study selection and data collection process were conducted by all authors. Disagreements regarding study selection and data extraction were resolved through consensus-based discussion.

2.5. Risk of Bias Assessment

Two independent reviewers critically assessed the included studies using The Joanna Briggs Institute’s critical assessment tool for case reports (8). The presence of bias was determined for each article using the checklist of eight questions included in Table 2. The articles received a score to indicate their degree of bias (low (included) and high (excluded)). For the purpose of this study, if “yes” was answered for more than half of the eight questions on the checklist, the study was considered to have a low risk of bias. Otherwise, answering “no” or “unclear” to half or more of the eight questions means the study was ascertained to have a high risk of bias and was excluded from this systematic review. Discrepancies in quality ratings were resolved through consensus-based discussion.

3. Results

3.1. Study Selection and Characteristics

Five databases were used to find articles related to the use of corticosteroid in myocarditis associated with COVID-19. We found 3479 articles; out of which, eighteen case reports were then deemed eligible for inclusion in the present study (9–26). A PRISMA flow diagram detailing the process of identification, screening, inclusion, and exclusion of studies is shown in Figure 1. The mean age of the reported patients was 47.8±13.2 years (range 18–69 years). There was no gender predominance. Most of the reported cases were from USA (39%) followed by Spain, China, and UK (11% each), while Brazil, Colombia, France, Belgium, and Italy contributed one case each. Various corticosteroids were used but the most commonly applied were methylprednisolone (89%), hydrocortisone (5.5%), and prednisolone (5.5%). The most common route of administration among the studies was intravenous administration and the duration of treatment varied between one and fourteen days. Other drugs were also used as combination therapy along with corticosteroids. Table 1 recounts the characteristics of the included studies.

3.2. Risk of Bias within Studies

All articles were determined to have low risk of bias. Seven other studies were identified as having high risk of bias and were excluded from the final inclusion process. Overall, studies did not report the adverse events resulting from the interventions. Moreover, low-level evidence from the included...
studies could not explain the causal relationship between the interventions and the outcomes. A complete risk of bias assessment of the comprised studies is displayed in Table 2.

4. Discussion

Eighteen case reports administering corticosteroids to subjects with myocarditis associated with COVID-19 were included in this systematic review. These case reports described several types of corticosteroids, doses, routes of administration, and various outcomes. For instance, in the Colombian study conducted by Bernal-Torres et al. (9), the authors described a 38-year-old woman without any comorbid conditions presenting with palpitations as well as general malaise since 3 days prior to admission. The patient had positive PCR examination on nasal swab for COVID-19. Furthermore, the patient was diagnosed with fulminant myocarditis associated with COVID-19 and was treated with intravenous immunosuppressant in the form of methylprednisolone. As a result, the patient experienced clinical improvement and was discharged on day 16. Case reports with similar population, without comorbid conditions, and with similar steroid therapy regimen were also provided by Garau et al. (12), Hu et al. (13), and Naneishvili et al. (19). They showed progressive clinical improvements in various aspects. Higher dose of methylprednisolone was also found to provide good clinical improvements in studies performed by Salamanca et al. (22) and Sampaio et al. (23). Some patients with certain comorbidities such as hypertension (11, 18), heart failure (15), and type 1 diabetes mellitus (21) showed clinical improvements as well. In addition, there were also various studies that did not specify the steroid dose used (14, 16). Besides, it was not uncommon to use other types of corticosteroids such as hydrocortisone (11) as well as oral prednisolone (24), which provided good clinical improvements as well.

Each and every study used other therapeutic agents, such as antibiotics (67%), hydroxychloroquine (50%), immunoglobulin (38%), antiviral drugs (27%), immunomodulators (27%), colchicine (22%), and other agents in addition to corticosteroid therapy to manage myocarditis associated with COVID-19 in patients. Regarding the outcomes, at the time of submission of those case reports, the majority of patients had survived (72%). Most of the patients who reportedly passed away were noted to have both acute respiratory distress syndrome (ARDS) and multiple-organ failure (Table 1). Most of the cases in this study were reported in sufficient detail; however, four reports did not specify the dose of the corticosteroid used and three of them did not report the duration of the corticosteroid’s usage. The use of corticosteroids in myocarditis associated with COVID-19 seemed to have a better outcome in this small study. From the majority of those who got myocarditis from COVID-19 infection, good outcomes were reported more in those undergoing corticosteroid therapy (thirteen out of eighteen patients) compared with those who did not take a corticosteroid (five out of eighteen patients).

The plausible explanation for these is that according to current researches, higher concentration of proinflammatory cytokines and chemokines were detected in patients with multiple organ dysfunction syndrome associated with COVID-19 due to exaggerated immune response to the virus (27). Based on this mechanism, corticosteroids can be clinically utilized to prevent the immune system from attracting more inflammatory cells to the tissue e.g. cardiac, which reduces inflammation (28).

Recently, the European Society of Cardiology has issued a guidance in dealing with cardiovascular manifestations of COVID-19, yet there is no clear recommendation for the treatment of myocarditis associated with SARS-CoV-2 (29). Myocarditis is a potentially life-threatening disease. For this reason, from the current evidence that was drawn from this systematic review, the authors of this study proposed that corticosteroid must be considered as a last resort in terms of treating patients with myocarditis associated with COVID-19. This systematic review pooled case reports of patients with myocarditis caused by COVID-19 infection. Since this is a pooled case report, the evidence is weaker than controlled clinical trials. The number of cases was also small; there were only 18 cases from 18 studies. The findings of the pooled case reports might not apply to all patients, and the level of evidence is low. Secondly, the observed outcomes cannot be solely attributed to the corticosteroid therapy due to the combination of multiple drugs. This systematic review is a hypothesis-generating study. Further investigation needs to be done to obtain consecutive samples in a controlled study where the patients are blinded to corticosteroid therapy group and control group. However, the rarity of this event may impede such effort. In that case, the need for reviewing this matter in a systematic way was considered by the authors although good level of evidence were limitedly available.

5. Conclusion

The current systematic review showed that the use of corticosteroid agents is beneficial in improving the outcome of myocarditis associated with COVID-19. The present study showed that no randomized clinical trial has been performed with the aim of assessing the efficacy and safety of using corticosteroids for treating myocarditis associated with COVID-19, thus well-established randomized clinical trials should be pursued in order to confirm the findings of the present review.
6. Declarations

6.1. Authors’ Contributions
WK helped in the conception and design of the study. WK, N, CMJ, RBM, AGN, and SD were actively involved in literature search, study selection, data extraction, extensive review, and writing the manuscript. All authors read and approved the final submitted version.

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6.4. Conflict of Interests
The authors report no financial relationships or conflicts of interest regarding the content herein.

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| Authors            | Year   | Gender | Complete Assessment                                                                 | Corticosteroid             | Dose         | Route | Duration | Other Medication(s)                                                                 | Outcome(s)                                                                 |
|--------------------|--------|--------|--------------------------------------------------------------------------------------|----------------------------|--------------|-------|----------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Bernal-Teves et al.| 2020   | Female | Fulminant myocarditis associated with COVID-19, cardiogenic shock, and COVID-19 pneumonia | Methylprednisolone         | 200 mg/d     | IV    | 12 days  | Intravenous human immunoglobulin, hydroxychloroquine, azithromycin, lopinavir/ritonavir, norepinephrine, dobutamine, and levosimendan on first day of admission | Clinical improvement, discharged on day-16                                  |
| Doyle et al.       | 2020   | Male   | Myocarditis and severe acute respiratory distress syndrome related to COVID-19        | Methylprednisolone         | 1000 mg/d    | IV    | 4 days   | Hydroxychloroquine, azithromycin, ceftriaxone, colchicine, tocolizinam                        | Clinical improvement, discharged on day-19                                   |
| Doyen et al.       | 2020   | Male   | Myocarditis associated with COVID-19, hypertension                                   | Methylprednisolone         | 1 mg/kg/d    | IV    | 1 day    | Aspirin, furosemide                                                                 | Clinical improvement, discharged on day-21                                   |
| Guaran et al.      | 2020   | Female | Fulminant myocarditis associated with COVID-19, cardiogenic shock, and COVID-19 pneumonia | Methylprednisolone         | 200 mg/d     | IV    | 8 days   | Intravenous human immunoglobulin, hydroxychloroquine, antibiotics                      | Clinical improvement, discharged on day-45                                   |
| Hu et al.          | 2020   | Male   | Fulminant myocarditis associated with COVID-19, cardiogenic shock, and COVID-19 pneumonia | Methylprednisolone         | 200 mg/d     | IV    | 4 days   | Intravenous human immunoglobulin, piperacillin-sulbactum, pantoprazole, Norepinephrine, diuretic, Methylprednisolone | Clinical improvement, discharged on day-21                                   |
| Hussain et al.     | 2020   | Male   | Fulminant myocarditis associated with COVID-19, hypertension                          | Methylprednisolone         | N/A          | IV    | N/A      | Dobutamine, indomethacin, azithromycin, hydroxychloroquine, remdesivir, colchicine       | Deteriorated after seventh day of admission                                |
| Incardi et al.     | 2020   | Female | Myocarditis associated with COVID-19, heart failure                                   | Methylprednisolone         | 1 mg/kg/d    | IV    | 3 days   | Intravenous aspi, hydroxychloroquine, lipinavir/ritonavir                              | Progressive clinical and hemodynamic improvement                             |
| Khalid et al.      | 2020   | Female | Myopericarditis associated with COVID-19, pericardial effusion, and cardiogenic shock | Methylprednisolone         | Not specified | Oral | 3 days   | Calcine, dobutamine, norepinephrine                                                  | Clinical improvement, discharged on day-9                                    |
| Khatri et al.      | 2020   | Male   | Pericardial myocarditis associated with COVID-19, cardiogenic and distributive shock with multi-organ failure | Methylprednisolone         | 200 mg/d     | IV    | 2 days   | Dobutamine, vasopressin, norepinephrine, hydroxychloroquine, vancomycin, azithromycin, cefepime, and intraavenous human immunoglobulin | Death due to multi-organ failure                                            |
| Li et al.          | 2020   | Male   | COVID-19-induced myopericarditis, cardiogenic shock, hypertension, and hyperlipidemia | Methylprednisolone         | 1000 mg/d    | IV    | 3 days   | Methylprednisolone                                                                  | Clinical improvement, discharged on day-52                                   |
| Saneidivit et al.  | 2020   | Female | Fulminant myocarditis associated with COVID-19, cardiogenic and distributive shock with multi-organ failure | Methylprednisolone         | 1000 mg/d    | IV    | 3 days   | Methylprednisolone                                                                  | Clinically improved, echocardiography result improved                       |
| Ortiz et al.       | 2020   | Female | Fulminant myocarditis due to COVID-19, hypertension, cervical degenerative arthropathy, chronic lumbar radiculopathy, lymph node tuberculosis | Methylprednisolone         | 500 mg/d     | IV    | 14 days  | Intravenous human immunoglobulin, antiviral treatment consisting of IFNB, and ritonavir/lopinavir | Deteriorated with rapid clinical progression to cardiogenic shock. Normal biomtricial function was regained within a few days, with severe subsequent dyspnea that required continued ECMO | |
| Richard et al.     | 2020   | Female | Fulminant myocarditis associated with COVID-19, diabetes mellitus type 1 with multiple previous episode of diabetic ketoacidosis, diabetic gastroparesis, glaucoma, anemia, depression | Methylprednisolone         | 1 g/d        | IV    | 3 days   | Dobutamin, norepinephrine, heparin, insulin, potassium, vancomycin, and piperacillin/tazobactum | Clinically improved on the third day following corticosteroid administration |
| Salimanc et al.    | 2020   | Male   | Fulminant myocarditis associated with COVID-19, cardiogenic shock                     | Methylprednisolone         | 1000 mg/d    | IV    | 4 days   | Thrombolysis, hydroxychloroquine, azithromycin, and lipinavir-ritonavir               | Clinical status improved                                                   |
| Sampao et al.      | 2020   | Female | Fulminant myocarditis associated with COVID-19, cardiac tamponade, and refractory circulatory shock | Methylprednisolone         | 50 mg/d      | Oral  | 12 days  | Hydrogen, creatine phosphate, colchicine                                                | Clinical improvement, discharged on day-13                                   |
| Chabbir et al.     | 2020   | Male   | Fulminant myocarditis associated with COVID-19, severe pneumonia, ARDS, and multiple organ dysfunction syndrome (MODS) | Methylprednisolone         | Not specified | IV    | N/A      | Norepinephrine, furosemide, cefepime, doxycycline, hydroxychloroquine, enoxaparin    | Death                                                                       |
| Zing et al.        | 2020   | Male   | Fulminant myocarditis associated with COVID-19, severe pneumonia, ARDS, and multiple organ dysfunction syndrome (MODS) | Methylprednisolone         | N/A          | N/A   | N/A      | Lopinavir-ritonavir, interferon α-1b, immunoglobulin, piperacillin-tazobactum          | The patient died on the 35th day of hospitalization                         |

Abbreviations: kgBW: Kilogram Body Weight; N/A: Not Available; ECMO: Extracorporeal Membrane Oxygenation; IV: intravenous; ARDS: acute respiratory distress syndrome.
Table 2: Assessment of the risk of bias of the included studies

| Authors          | Were patient’s demographic characteristics clearly described? | Was the patient's history clearly described and presented as a timeline? | Was the current clinical condition of the patient on presentation clearly described? | Were diagnostic tests or assessment methods and the results clearly described? | Was the intervention(s) 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 Risk of Bias |
|------------------|-------------------------------------------------------------|------------------------------------------------------------------------|-------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------|----------------------------------------------------------------------------------------|---------------------------------------------|------------------|
| Bernal-Torres et al. | Yes                                                        | Yes                                                                    | Yes                                                                                 | Yes                                                                            | Yes                                                                    | Unclear                                                             | Yes                                                                                      | 87.5%                                                                   | Low              |
| Coyle et al.      | Yes                                                        | Yes                                                                    | Yes                                                                                 | Yes                                                                            | Yes                                                                    | Unclear                                                             | Yes                                                                                      | 87.5%                                                                   | Low              |
| Doyen et al.      | Yes                                                        | Yes                                                                    | Yes                                                                                 | Unclear                                                                       | Yes                                                                    | No                                                                  | Yes                                                                                      | 75%            | Low              |
| Hu et al.         | Yes                                                        | Yes                                                                    | Yes                                                                                 | Yes                                                                            | Yes                                                                    | Unclear                                                             | No                                                                                       | 87.5%                                                                   | Low              |
| Hussain et al.    | Yes                                                        | No                                                                     | Yes                                                                                 | No                                                                             | Yes                                                                    | Unclear                                                             | Yes                                                                                      | 82.5%                                                                   | Low              |
| Inglund et al.    | Yes                                                        | Yes                                                                    | Yes                                                                                 | Yes                                                                            | Yes                                                                    | Yes                                                                 | Yes                                                                                      | 100%           | Low              |
| Khalid et al.     | Yes                                                        | Yes                                                                    | Yes                                                                                 | Unclear                                                                       | Yes                                                                    | Yes                                                                 | Yes                                                                                      | 87.5%                                                                   | Low              |
| Khatri et al.     | Yes                                                        | Yes                                                                    | Yes                                                                                 | Yes                                                                            | Yes                                                                    | Unclear                                                             | Yes                                                                                      | 87.5%                                                                   | Low              |
| Li et al.         | Yes                                                        | Yes                                                                    | Yes                                                                                 | Yes                                                                            | Yes                                                                    | Unclear                                                             | Yes                                                                                      | 87.5%                                                                   | Low              |
| Naneishvili et al.| Yes                                                        | Yes                                                                    | Yes                                                                                 | Yes                                                                            | Yes                                                                    | Unclear                                                             | Yes                                                                                      | 87.5%                                                                   | Low              |
| Ortiz et al.      | Yes                                                        | Yes                                                                    | Yes                                                                                 | Yes                                                                            | Yes                                                                    | Yes                                                                 | Yes                                                                                      | 100%           | Low              |
| Richard et al.    | Yes                                                        | Yes                                                                    | Yes                                                                                 | Yes                                                                            | Yes                                                                    | Unclear                                                             | Yes                                                                                      | 87.5%                                                                   | Low              |
| Salmaschi et al.  | Yes                                                        | Yes                                                                    | Yes                                                                                 | Yes                                                                            | Yes                                                                    | Unclear                                                             | Yes                                                                                      | 87.5%                                                                   | Low              |
| Sampaio et al.    | Yes                                                        | Yes                                                                    | Yes                                                                                 | Unclear                                                                       | Yes                                                                    | Unclear                                                             | Yes                                                                                      | 87.5%                                                                   | Low              |
| Shaibhri et al.   | Yes                                                        | Yes                                                                    | Yes                                                                                 | Yes                                                                            | Yes                                                                    | No                                                                  | Yes                                                                                      | 87.5%                                                                   | Low              |
| Tavares et al.    | Yes                                                        | Yes                                                                    | Yes                                                                                 | Unclear                                                                       | Yes                                                                    | No                                                                  | Yes                                                                                      | 75%            | Low              |
| Zeng et al.       | Yes                                                        | Yes                                                                    | Yes                                                                                 | Unclear                                                                       | Yes                                                                    | Yes                                                                 | Yes                                                                                      | 87.5%                                                                   | Low              |

All articles were published in 2020.
Figure 1: Flow chart of study selection.

Records identified through database searching (n = 3479)

Records after duplicates removed (n = 3414)

Records screened (n = 3414)

Records excluded based on title and/or abstract (n = 3236)

Full-text articles excluded, with reasons (n = 160)
- Diagnosis not relevant n = 32
- Design studies n = 30
- Intervention not mentioned n = 97
- Animal study n = 1

Full-text articles assessed for eligibility (n = 178)

Studies included in qualitative synthesis (n = 18)