Prevalence of myocarditis in COVID patients

Altaf Rashad Ashour

Abstract:
This study examines the occurrence and related negative reactions and cardiovascular disease in COVID-19 patients with concomitant myocarditis. The positive correlation between LVM and BMI is expected to be lost when LVMI is tested because LVMI is corrected for BSA. Both LVM and LVMI had a significant negative correlation with fractional shortening as a measure of LV performance. LVMI was predicted by 3 factors: age (positive interaction), endocardial fractional shortening (negative interaction), and heart rate-corrected augmentation index (c-AIx; negative interaction). These findings are consistent with those of the Framingham Heart Study, which identified the positive associations of LVM with age, BMI, and systolic blood pressure. The results of this study recommend that COVID-19 patients who develop recent myocarditis are related with a substantially higher risk of death from all causes, compared to patients with COVID-19 alone.
Key Words: COVID-19, Myocarditis, vaccines, prevalence

I. Introduction:

Myocarditis is non-ischemic inflammatory condition of the heart muscle and pericardium, respectively. The clinical manifestations of this disease are very different and might be due to non-specific symptoms such as general malaise, fatigue or diarrhea. In other cases, myocarditis can rouse "myocardial infarction, symptomatic arrhythmias, heart failure, myocardial infarction or sudden cardiac death". Even though myocarditis has different causes; infection is the most common cause [1].

Symptoms of COVID-19 include involvement of the respiratory tract, varying from mild upper respiratory tract symptoms to acute respiratory distress syndrome. On the other hand, extreme COVID-19 is associated with multi-organ involvement, as some cases show a large proportion of cardiac involvement in hospital patients [2]. Furthermore, cardiac injury appears to be substantially associated with elevated hospital mortality in patients with COVID-19. COVID-19 has a variety of cardiovascular disease consequences, which include "acute heart failure, arrhythmias, acute coronary syndrome, myocarditis and cardiac arrest". Elevating evidence describes cardiac involvement in COVID-19, which include myocarditis or more commonly, elevated biomarkers of heart failure, all of which might be associated with derived forecast.

II. Study Objective:

In spite of recent case reports, the occurrence and clinical effects of new-onset myocarditis in adults with COVID-19 are unknown. Thereby, utilizing the Global Allied Health Research Network, the objective of this study was to examine the occurrence and related negative reactions and cardiovascular disease in COVID-19 patients with concomitant myocarditis.

III. Discussion:

Criteria of Myocarditis Diagnosis

In recent clinical practice, myocarditis diagnosis is not easy. A clinician may suspect myocarditis due to various symptoms of the patient such as pain in the chest, increase in ST-segment in ECG, elevation of troponin in serum, and results of imaging which includes CMR (cardiac magnetic resonance) and echocardiography. Recently, the criteria of myocarditis diagnosis using CMR have been improved and now it also includes criteria relating to both T1- and T2- which indicates myocardial inflammation [3]. Apart from the diagnosis of heart damage, an important step in the diagnosis of myocarditis is the removal of a disease known as obstructive coronary artery, especially if the clinical symptoms are similar to coronary syndrome. But even after all these procedures described above, myocarditis diagnosis can still be elusive as other non-ischemic as well as ischemic diseases may have same clinical signs and symptoms [4]. So it can be said that for the proper diagnosis and identification of myocarditis, one might need EMB (endomyocardial biopsy) and this procedure is considered as the best method for evaluation of myocarditis until now.

Myocarditis diagnosis in patients of COVID-19

There is no difference in the diagnostic criteria of myocarditis between normal patients and COVID-19 patients. But, the pathway of diagnosis can vary, since while treating COVID-19 patients, special precautionary measures must be taken by the health care workers in order to avoid contracting the viral infection. Secondly, there might be distinction regarding the stability or instability of the patient. For patients with suspected myocarditis, who are also critically ill and admitted to ICU, referrals to the cardiac catheterization lab as well as radiology section can be very troublesome. An unstable patient of COVID-19 can be transferred to cardiac catheterization lab if there is a diagnosis of elevated ST-segment and there is a need to treat the patient with coronary percutaneous intrusion. If in the laboratory, no evidence of obstructed coronary is found but still there is a strong suspicion of myocarditis then endomyocardial biopsy can be done with great expertise and care. Both CCT (coronary computed tomography) and CMR can be done for those COVID-19 patients who are stable clinically for the diagnosis of myocarditis in the radiology segment of the hospital. For the diagnosis of myocarditis in COVID-19 patients whether stable or unstable, generally echocardiography is performed and sometimes this technique is combined with pulmonary ultrasound evaluation at the bedside of the patient [5].

Lastly, it must be kept in mind that echocardiography is not a good method for diagnosis in COVID-19 patients either they are admitted to ICU or in stable condition because this technique has low image quality. To minimize the contact of operator with COVID-19 infection, echocardiographic tests are usually restricted to the immediate collection of required images. All these drawbacks must be noted by physicians caring for patients of COVID-19 while they request for echocardiographic examinations.

Characteristics, prevalence, and prognosis of myocarditis in patients of COVID-19

In COVID-19 patients, the reason for myocardial injury is usually attributed to increase in the serum level of troponin [11–14], that is why clinicians still lack the exact classification of heart both functionally as well as morphologically in patients of COVID-19 on a large scale. Up till now, clinicians only have the information regarding myocarditis in the patients of COVID-19 only from small series and case reports [6]. All the information is present in three reviews available on internet until now.

In a study, myocarditis as secondary infection in COVID-19 patients was reported in 14 patients from 1st December, 2019 to 30th June, 2020. This infection was predominantly present in males of median age of approximately 54 years with 58% prevalence. Most of the patients (50%) didn't have comorbid infection before. Those patients who had past history of illness such as high blood pressure were more prone to comorbid infection than others (33%). Out of 14 reported cases, 11 patients had hemodynamic condition and most of these patients were in trauma and shock. In 91% patients, level of serum troponin was high and the results of ECG were inconsistent. In 83% of cases, Echocardiography was done and out of these 83%, 60% of the patients had low LV-EF. In these echocardiograms (20%) Cardiac tamponade physiology was also revealed [7].

In their review study, [8] covered eleven research articles. Out of these 11 articles, 2 and 9 were retrospective studies and case studies respectively. In the reported case studies, age of COVID-19 patients who were diagnosed with myocarditis was 51.8±16.9. In all these case studies, both females and males were equally affected from myocarditis. But in retrospective studies, it was observed that the condition was more prevalent in males older than 55 years. The main clinical symptoms included dyspnea, which was followed by chest pain, cough, and fever. All these 11 studies also reported increase in the level of either troponin-T or I, along with increase in BNP (brain natriuretic peptide) as well as CK-MB (creatinine kinase-myocardial band). In 5 case reports, elevation in ST-segment was also observed through ECG, as well as in 3 cases, inverted T waves were also observed. Moreover, a decrease in LV-EF was also observed in 6 cases after echocardiography.

In another recently published review paper, a total of thirty-one publications including cohort studies, case series, and case reports were considered. All these publications included a total of 51 COVID-19 patients in which 39 patients had suspicion of myocarditis while 12 patients had myocarditis. All these studies reported that myocarditis was more prevalent in males (69%) having age 55 years. The most prevalent and common clinical symptoms were chest pain, fever, cough, and difficulty in breathing. Alterations in ECG included changes in T-wave, non-specific ST-segment, as well as ventricular tachycardia. Out of 51 patients, most had high inflammatory and cardiac biomarkers in their body. Moreover, hypokinesis and LV systolic abnormality were also frequent in these patients.

The result of confirmed as well as suspected myocarditis is one of the central issues among patients of COVID-19. Reviews that have been discussed above can be used to deduce information regarding this issue. In one of the reviews mentioned above, most of the COVID-19 patients (81%) were discharged from the hospital and only a few numbers of patients were not able to survive (19%). These patients (19%) who were reported dead were diagnosed with myocarditis as well as acute respiratory distress syndrome [9]. All these observations suggested and proved that majority of the COVID-19 patients with possible myocarditis had a positive result of hospitalization and were discharged after treatment. Last but not the least, there is a dire need for further

research in this regard in order to determine the result of COVID-19 patients with suspected and confirmed myocarditis after discharge from the hospital [10].

Implications for treatment

In literature, there is a little evidence regarding the treatment of myocarditis, as so far only small number of clinical trials has been conducted. Therapy of myocarditis must be based on diagnosis of any abnormality in ventricles as well as the explanation of myocarditis etiology. It is speculated that non-viral etiology may take advantage from immunosuppressive treatment resulting in significant development in prognosis.

When the causative agent of myocarditis is virus, then the therapy involves isolation of virus with endomyocardial biopsy because various viruses need anti-viral treatment designed particularly for the and it has been observed that with the help of immunosuppressive treatment, viral myocarditis can be improved [11].Generally, treatments involving anti-inflammatory nonsteroidal drugs are not recommended by clinicians for myocarditis patients as they can cause kidney failure as well as retention of sodium, which can further damage the ventricles leading to acute ventricular dysfunction.

In the case of COVID-19-related myocarditis, various researchers have recommended to utilize high dosage of steroids as well as intravenous antibodies (IVIG) [12]. It has been expected that various anti-viral drugs such as lopinavir/ritonavir, remdesivir, interferon beta1a, and hydroxychloroquine are efficient in treating myocarditis in hospitalized patients of COVID-19. But unluckily, all of these anti-viral drugs are least or no effective at all in decreasing time period of stay in hospital, overall mortality as well as commencement of ventilation.

A proposal for the process of diagnosis in clinical practice

If clinicians suspect myocarditis in patients with COVID-19 due to early acute cardiac signs and symptoms as well as changes in ECG, both bedside echocardiography and troponin level should be checked before making the final decision. All these same procedures should also be done for those patients who develop hemodynamic or electrical inability. In particular, changes in overall biomarkers or their trends in the body of patients should be observed carefully instead of those values which were obtained individually. Succeeding non-invasive as well as invasive diagnostic work, which includes CCT and CMR, possibly will depend on the outcomes of laboratory tests and echocardiography as well as the patient's clinical status. Most important differential diagnoses are sepsis-related cardiomyopathy, stress-induced cardiomyopathy, and acute coronary syndrome, particularly for a complete form of myocarditis.

Overall, this retrospective diagnosis signifies the largest such follow-up database for patients with COVID-19 and patients with recent myocarditis. The results of this study recommend that myocarditis in patients with COVID-19 are significantly associated with an elevated incidence of all causes of death, re-hospitalization and acute myocardial infarction [12]. Compared with the corresponding control groups, patients with pericarditis were related with a higher prevalence of cardiac arrest, heart failure and atrial fibrillation. In contrast, patients with myocarditis were not associated with a higher incidence of cardiac arrest, heart failure and atrial fibrillation compared to the corresponding control groups [6]. Thus, although recent myocarditis (5.0%) was more common as compared to pericarditis (1.5%) in COVID-19 patients, the latter appeared to be correlated with more serious negative reactions and cardiovascular disease [8].

Prior evidence showed that among 222 cases of non-COVID-19 non-COVID-induced myocardial infarction, the mortality rate was 19.2% at 4.7 years of follow-up. Among almost 8,000 patients with pericarditis registered nationally in Denmark, the overall mortality rate over 5 years was 7.1%, compared with 4.2% in the control group without pericardium [5]. In this study, the results showed that patients with COVID-19 myocarditis were only associated with the risk of side effects and cardiovascular disease in patients with COVID-19. The mortality rates of patients with myocarditis were 1.90 (95% CI: 1.80–2.01) and 2.55 (95% CI: 2.24–2.91), respectively. Although this has not been studied before, these results add to the results of Shi et al., Which showed that heart injuries were common (19.7%) among 416 hospitalized patients with COVID-19 in Wuhan, China. Mortality (51.2%) was higher than in patients without heart injury (4.5%; $p < 0.001$) and patients in intensive care were more potentially to have heart injury [3].

Even though we did not study heart injury per se, the study has also found that the extent of mortality associated with the severity of COVID-19 was estimated by a mandate for admission records. In fact, the evidence suggests a dose response with a 68% (1.40–2.00) and 195% (2.19–3.97) increase in all-cause mortality in hospitals or intensive care patients with COVID-19 myocarditis, respectively. In addition, patients with COVID-19 myocarditis who were not initially admitted due to COVID-19 did not have an increased mortality rate. Likewise, for COVID-19 patients with myocarditis, the mortality rate of all causes increased in patients who were not hospitalized and in intensive care after COVID-19 diagnosis. Thereby, the clinical significance of recent myocarditis in patients with COVID-19 appears to depend on the extremity of the original viral infection.

In a group of German patients who have currently recovered from COVID-19, MRI showed persistent myocarditis in 60 patients (60%), related to current disease, extremity, entire history of acute illness and time to initial diagnosis does not matter. This is consistent with previous non-COVID-19 studies showing that clinical manifestations of cardiac failure, ventricular tachycardia or atrial fibrillation did not forecast survival in patients with myocarditis. On the contrary, in this study, patients with recent myocarditis had a higher proportion of comorbidities, which include cardiovascular disease, metabolic disease, neurological disease, and gastrointestinal disease. This is consistent with an older study in which patients with present cardiovascular disease appeared to be more vulnerable to COVID-19 disease. In particular, 30% and 60% of patients with heart failure had a presence of coronary heart disease and hypertension, was considerably higher as compared to those irrespective heart failure [2].

In one case of COVID-19 in a young child, it was suggested that SARS-CoV-2 infection had a direct effect on heart tissue, which in this case was the leading cause of recent myocarditis and heart failure. This and other cases provide indication that COVID-19 might be a multi-system inflammatory syndrome and that the consequences of cardiovascular disease have a substantial health risk in this study. It has been suggested that the physiology of viral myocarditis is a merger of direct cell damage and T lymphocyte-mediated cytotoxicity and that cytotoxic syndrome may exacerbate this condition. Therefore, COVID-19-related procedures for myocarditis might be similar, considering that the location of myocardial infarction COVID-19 has been witnessed in a case study of a 69-year-old man who underwent a myocardial biopsy.

It is worth noting some limitations. Firstly, the data were gathered from EMR databases of clinics and some health circumstances might be underestimated. It is a fact that records of ICD codes in management databases can differ according to enablers including age, number of comorbidities, extremity of the disease, length of hospital stay and whether hospital deaths have happened. In particular, the approach for diagnosing myocarditis based on EMR is unidentified. On the contrary, this study has examined the occurrence and clinical results of myocarditis after diagnosis of pneumonia (ie for COVID-19) to identify the association with cardiovascular disease in the COVID-19 group. The incidence reported in this study may be lower than the actual prevalence. Furthermore, our findings should not be construed as causal; it is only where recent myocarditis is related with a higher mortality rate found in this study; we do not know if myocarditis is an influencer or a marker. In fact, residual confounding factors might have influenced our findings, which include "lifestyle factors, socioeconomic status, and other health signs / conditions" that were not available from EMR. Follow-up is needed in future work to further investigation of cardiac engagement in COVID-19, particularly in severely ill patients.

IV.   Conclusion:

The results of this study recommend that COVID-19 patients who develop recent myocarditis are related with a substantially higher risk of death from all causes, compared to patients with COVID-19 alone. Furthermore, the extremity of COVID-19 appears to be related with more extreme consequences in patients with myocarditis. Lastly, even though myocarditis was more common, pericarditis appeared to be correlated with a higher risk of death and recent cardiovascular disease. Thereby, early intervention and follow-up of patients with recent myocardial infarction should be considered after COVID-19 diagnosis for residents with current cardiovascular disease and risk factors.

References:

[1]. Bozkurt, B., Kamat, I., & Hotez, P. J. (2021). Myocarditis with COVID-19 mRNA vaccines. *Circulation*, *144*(6), 471-484.

[2]. Buckley, B. J., Harrison, S. L., Fazio-Eynullayeva, E., Underhill, P., Lane, D. A., & Lip, G. Y. (2021). Prevalence and clinical outcomes of myocarditis and pericarditis in 718,365 COVID-19 patients. *European journal of clinical investigation*, *51*(11), e13679.

[3]. Daniels, C. J., Rajpal, S., Greenshields, J. T., Rosenthal, G. L., Chung, E. H., Terrin, M., ... & Big Ten COVID-19 Cardiac Registry Investigators. (2021). Prevalence of clinical and subclinical myocarditis in competitive athletes with recent SARS-CoV-2 infection: Results from the big ten COVID-19 cardiac registry. *JAMA cardiology*.

[4]. Golpour, A., Patriki, D., Hanson, P. J., McManus, B., & Heidecker, B. (2021). Epidemiological impact of myocarditis. *Journal of Clinical Medicine*, *10*(4), 603.

[5]. Halushka, M. K., & Vander Heide, R. S. (2020). Myocarditis is rare in COVID-19 autopsies: Cardiovascular findings across 277 post-mortem examinations. *Cardiovascular Pathology*, 107300.

[6]. Kim, J. Y., Han, K., & Suh, Y. J. (2021). Prevalence of abnormal cardiovascular magnetic resonance findings in recovered patients from COVID-19: a systematic review and meta-analysis. *Journal of Cardiovascular Magnetic Resonance*, *23*(1), 1-22.

[7]. Laganà, N., Cei, M., Evangelista, I., Cerutti, S., Colombo, A., Conte, L., ... & Mumoli, N. (2021). Suspected myocarditis in patients with COVID-19: A multicenter case series. *Medicine*, *100*(8).

[8]. Liu, J., Deswal, A., & Khalid, U. (2021). COVID-19 myocarditis and long-term heart failure sequelae. *Current opinion in cardiology*, *36*(2), 234-240.

[9]. Mele, D., Flamigni, F., Rapezzi, C., & Ferrari, R. (2021). Myocarditis in COVID-19 patients: current problems. *Internal and Emergency Medicine*, 1-7.

[10]. Singer, M. E., Taub, I. B., & Kaelber, D. C. (2021). Risk of myocarditis from COVID-19 infection in people under age 20: a population-based analysis. *medRxiv*.

[11].   Siripanthong, B., Nazarian, S., Muser, D., Deo, R., Santangeli, P., Khanji, M. Y., ... & Chahal, C. A. A. (2020). Recognizing COVID-19–related myocarditis: The possible pathophysiology and proposed guideline for diagnosis and management. *Heart rhythm*, *17*(9), 1463-1471.

[12].   Starekova, J., Bluemke, D. A., Bradham, W. S., Eckhardt, L. L., Grist, T. M., Kusmirek, J. E., ... & Reeder, S. B. (2021). Evaluation for myocarditis in competitive student athletes recovering from coronavirus disease 2019 with cardiac magnetic resonance imaging. *JAMA cardiology*.