The incidence of myocarditis and pericarditis in post COVID-19 unvaccinated patients

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Abstract—Background and Aim: Viral infections have also been associated with the presence of autoimmune diseases such as systemic lupus disease, rheumatoid arthritis, and diabetes mellitus. SARS-CoV-2 gains entry into human cells by binding its spike protein to the membrane protein angiotensinconverting enzyme 2 (ACE2). It has recently been reported that the incidence of myocarditis and pericarditis is increased in COVID-19 patients during the acute illness. However; whether or not myocarditis and pericarditis after the recovery period are a part of the long COVID-19 syndrome is yet unknown. Hence, we studied the incidence of myocarditis and pericarditis in COVID-19 patients after recovering from the acute infection. Material and Methods: We retrieved records of all adult patients (age ≥ 18 years) who had a documented positive COVID-19 PCR test (n = 500) for the period of 1 year. A control group was created from a cohort of adult patients with at least one negative COVID-19 From this pool of patients, the control cohort was created by 3:1 matching of age (±2 years) and gender. Total 1000 patients in
control group were selected. Records included demography and cardiovascular risk factors: smoking status, obesity, diabetes mellitus, hyperlipidemia, CKD (chronic kidney disease), PVD (peripheral vascular disease), ACS (acute coronary syndrome), essential hypertension, CVA (cerebrovascular accident), and heart failure. Results: There was a slightly higher BMI with higher prevalence of obesity, diabetes mellitus, essential hypertension, cerebrovascular accidents and heart failure in the COVID-19 cohort. There was a lower prevalence of current and past smoking and peripheral vascular disease in the COVID-19 cohort. During the study period, five cases of myocarditis and 6 cases of pericarditis were detected in the COVID-19 cohort. Twelve cases of myocarditis and 15 cases of pericarditis were detected in the control cohort. Conclusion: Our data suggest that there is no increase in the incidence of myocarditis and pericarditis in COVID-19 recovered patients compared to uninfected matched controls. Further longer-term studies will be needed to estimate the incidence of pericarditis and myocarditis in patients diagnosed with COVID-19.

**Keywords**—acute coronary syndrome, COVID-19, myocarditis, pericarditis.

**Introduction**

The world has seen an emergence of a novel coronavirus disease 2019 (COVID-19), which has led to a global pandemic causing numerous hospitalizations and deaths. Healthcare systems have grappled with varied manifestations of the disease ranging from asymptomatic presentation to mild viral pneumonia and to those presenting with acute respiratory distress syndrome, stroke, and myocardial infarction. The pathogenesis of the disease involves entry of the virus through the respiratory system using the angiotensin-converting enzyme 2 (ACE2) as a receptor.¹

In addition to the clinical manifestations during the acute phase of the COVID-19 disease, there is an accumulating data regarding the subacute and long-term effects of COVID-19, also known as “post-acute COVID-19 syndrome” or “Long COVID”, defined by persistent symptoms several weeks after onset of COVID-19 infection.² The “Long-COVID” or “post-acute COVID-19 syndrome” is characterized by multi-organ sequelae or persistent symptoms after recovering from the acute COVID-19 phase, generally after 3 to 4 weeks from the onset of symptoms or the first PCR positive result test.³

The pathogenesis of “Long-COVID” may result from several mechanisms, including direct viral toxicity, hypercoagulability, microvascular injury, and angiotensin-converting enzyme maladaptation.⁴ While the underlying pathophysiological mechanisms leading to post-acute COVID-19 are yet to be fully understood, immune-mediated response⁵,⁶ and immune dysregulation are believed to play a major contributing role in the pathogenesis of this syndrome. Infectious causes have been shown to be an important inciting event in the
pathophysiology of autoimmune diseases.\textsuperscript{7} Viral infections have also been associated with the presence of autoimmune diseases such as systemic lupus disease, rheumatoid arthritis, and diabetes mellitus.\textsuperscript{8}

SARS-CoV-2 gains entry into human cells by binding its spike protein to the membrane protein angiotensinconverting enzyme 2 (ACE2).\textsuperscript{9} However, the spike protein must first be cleaved at the S1/S2 and subsequently at the S2’ sites to enable binding to ACE2. Cleavage at the S1/S2 site seems to be mediated by TMPRSS2, a serine protein.\textsuperscript{9} ACE2 can be found on the ciliated columnar epithelial cells of the respiratory tract, type II pneumocytes, and cardiomyocytes.\textsuperscript{10,11} Therefore, it is plausible that SARS-CoV-2 infects the human heart, especially in case of heart failure as ACE2 is upregulated,\textsuperscript{12} although the presence of viral receptors does not always predict tropism.\textsuperscript{13}

Several autoimmune phenomena were linked to a previous COVID-19 infection including heparin-induced thrombocytopenia (HITT), Kawasaki-like syndromes (MIS-C and MIS-A), Guillain-Barre syndrome, vasculitis, and thyroiditis.\textsuperscript{8} Thus, it can be postulated that the risk for autoimmune induced myocarditis and pericarditis is increased in recovering COVID-19 patients. It has recently been reported that the incidence of myocarditis and pericarditis is increased in COVID-19 patients during the acute illness.\textsuperscript{14} However; whether or not myocarditis and pericarditis after the recovery period are a part of the long COVID-19 syndrome is yet unknown. Herein, we studied the incidence of myocarditis and pericarditis in COVID-19 patients after recovering from the acute infection.

**Material and Methods**

We retrieved records of all adult patients (age ≥ 18 years) who had a documented positive COVID-19 PCR test (n = 500) for the period of 1 year. Records included demography and cardiovascular risk factors: smoking status, obesity, diabetes mellitus, hyperlipidemia, CKD (chronic kidney disease), PVD (peripheral vascular disease, ACS (acute coronary syndrome), essential hypertension, CVA (cerebrovascular accident), and heart failure. The post-COVID timeframe was defined from at least ten days after the date of positive PCR test contingent upon lack of symptoms related to COVID-19 infection. Patients with a first vaccination received before COVID-19 infection were excluded, resulting in the final COVID-19 cohort (n = 1500).

A control group was created from a cohort of adult patients with at least one negative COVID-19. From this pool of patients, the control cohort was created by 3:1 matching of age (±2 years) and gender. Total 1000 patients in control group were selected. The follow-up period of each of the three control patients was set to the exact same length of follow-up of the matched COVID-19 patient. The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2007) and then exported to data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). For all tests, confidence level and level of significance were set at 95% and 5% respectively.
Results

Total of 1500 study participants were included in the study. The mean standard deviation (SD) age in both groups was 42.9 (16.1) years, and 44.9% were males (Table 1). There was a slightly higher BMI with higher prevalence of obesity, diabetes mellitus, essential hypertension, cerebrovascular accidents and heart failure in the COVID-19 cohort. There was a lower prevalence of current and past smoking and peripheral vascular disease in the COVID-19 cohort.

During the study period, five cases of myocarditis and 6 cases of pericarditis were detected in the COVID-19 cohort. Twelve cases of myocarditis and 15 cases of pericarditis were detected in the control cohort. One out of the nine myocarditis patients were hospitalized due to severe COVID-19 infection with the need for mechanical ventilation, and myocarditis was diagnosed during the COVID-19 hospitalization at days 18 and 34 after infection, respectively. None of the patients who were diagnosed with pericarditis were hospitalized due to COVID-19 infection. The median (IQR) duration of hospitalization following myocarditis in the COVID-19 cohort was 6 days vs. 4 days in the control cohort (p > 0.05). The median (IQR) duration of hospitalization following pericarditis was 2.2 days in the COVID-19 cohort and 2.8 days in the control cohort (p > 0.05).

No statistical difference in the incidence rate of both myocarditis and pericarditis was observed between the COVID-19 cohort and the control cohort. In the multivariable Cox proportional hazards regression model, age and the male sex were independently associated with myocarditis. Obesity was borderline associated with myocarditis. Post COVID-19 infection was not associated with myocarditis. (Table 2)

Table 1: Baseline Characteristics of the study population by COVID-19 infection status

<table>
<thead>
<tr>
<th>Variables</th>
<th>COVID-19 (N=500)</th>
<th>CONTROL (N= 1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Year)</td>
<td>42.9 (16.1)</td>
<td>42.9 (16.1)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>235 (47)</td>
<td>470 (47)</td>
</tr>
<tr>
<td>Female</td>
<td>265 (53)</td>
<td>530 (53)</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>27.2 (6.8)</td>
<td>26.2 (7.2)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>390 (78)</td>
<td>690 (69)</td>
</tr>
<tr>
<td>Current</td>
<td>58 (11.6)</td>
<td>180 (18)</td>
</tr>
<tr>
<td>Past</td>
<td>52 (10.4)</td>
<td>130 (13)</td>
</tr>
<tr>
<td>Obesity</td>
<td>125 (25)</td>
<td>300 (30)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>55 (11)</td>
<td>130 (13)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>150 (30)</td>
<td>312 (31.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90 (18)</td>
<td>185 (18.5)</td>
</tr>
<tr>
<td>PVD</td>
<td>10 (2)</td>
<td>14 (1,4)</td>
</tr>
<tr>
<td>ACS</td>
<td>25 (5)</td>
<td>56 (5.6)</td>
</tr>
</tbody>
</table>
CKD = chronic kidney disease. PVD = peripheral vascular disease, CVA = Cerebrovascular Accident. ACS = acute coronary syndrome.

Table 2: Adjusted HRs for myocarditis and pericarditis

<table>
<thead>
<tr>
<th>Variables</th>
<th>Myocarditis</th>
<th>Pericarditis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>aHR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>COVID-19</td>
<td>1.04 (0.44–2.52)</td>
<td>0.2</td>
</tr>
<tr>
<td>Age</td>
<td>0.94 (0.92–1.01)</td>
<td>0.03*</td>
</tr>
<tr>
<td>Gender (Male)</td>
<td>4.39 (1.70–11.65)</td>
<td>0.001*</td>
</tr>
<tr>
<td>BMI</td>
<td>1.02 (0.95–1.05)</td>
<td>0.08</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.21 (0.22–4.98)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>0.29 (0.05–1.46)</td>
<td>0.09</td>
</tr>
<tr>
<td>Obesity</td>
<td>2.31 (0.99–5.41)</td>
<td>0.3</td>
</tr>
<tr>
<td>CKD</td>
<td>3.76 (0.85–17.60)</td>
<td>0.10</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.65 (0.61–4.15)</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.42 (0.32–5.4)</td>
<td>0.32</td>
</tr>
<tr>
<td>ACS</td>
<td>3.89 (0.72–20.31)</td>
<td>0.09</td>
</tr>
<tr>
<td>PVD</td>
<td>1.31 (0.09–12.79)</td>
<td>0.06</td>
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</tbody>
</table>

* indicates statistically significance at p≤0.05

Discussion

Myocarditis and pericarditis are well-known potential adverse reactions after mRNA-1273 and BNT162b2 vaccine administration. They are not widely recognized as possible adverse reactions of AstraZeneca COVID-19 vaccine, though the incidence of suspected myocarditis–pericarditis following mRNA and AstraZeneca COVID19 vaccine from the vaccine adverse event reporting system was similar (1.6–5.0 versus 2.0–3.7 per million doses, respectively). To date, only a few cases of myocarditis following exposure to the AstraZeneca COVID19 vaccine have been published. In the current large population study of subjects, who were not vaccinated against SARS-CoV-2, we observed no increase in the incidence of myocarditis or pericarditis from day 10 after positive SARS-CoV-2. Multivariable analysis did show male sex as associated with a higher risk of developing myocarditis or pericarditis, regardless of previous COVID-19 infection.
COVID-19 infection is responsible for considerable morbidity and mortality at an unprecedented scale globally. Recent studies suggest several mechanisms for the pathogenesis of the persistent and prolonged signs and symptoms associated with the cardiovascular system. Several earlier studies on SARS-CoV infections have highlighted the possible link between types of coronavirus infections and immune-mediated responses.\textsuperscript{19,20}

While the acute inflammation and injury to the heart are the current focus receiving attention, the long-term effects of healed myocarditis are completely unknown. Most infected patients experience mild, self-limiting symptoms; are managed in the community; and are not undergoing clinical testing such as ECG or cardiac imaging. Because the emphasis is evaluating and admitting patients with severe lower respiratory tract symptoms, many patients with possible myocarditis will never be evaluated. Some of these patients may survive the acute event but may be at risk for subsequent arrhythmias. In a study of patients with active and healed myocarditis, monomorphic ventricular tachycardia and regular ventricular arrhythmias were more frequent in those with healed than acute myocarditis.\textsuperscript{21} However, the presence of viral genomes on EMB was not associated with the occurrence of malignant arrhythmias.\textsuperscript{21}

Early in the COVID-19 pandemic, it was evident that COVID-19 patients with cardiovascular comorbidities have worse prognosis and higher in-hospital mortality.\textsuperscript{22} Individuals with underlying autoimmune diseases appear to be particularly vulnerable to severe sequelae resulting from COVID-19 infection.\textsuperscript{23} Other studies demonstrated that severe COVID-19 disease is associated with robust inflammatory responses including type two and hyper four hypersensitivity responses, resulting from overactivation of T cells and a subsequent cytokine storm.\textsuperscript{24,25} Immune-mediated manifestations of COVID-19 include mimicry of autoimmune diseases like Kawasaki disease, Guillain-Barre syndrome, vasculitis, myositis, and myocardial damage.\textsuperscript{26} Puntmann et al. found a 78% cardiac involvement assessed by Cardiac Magnetic Resonance Imaging (MRI) among patients with a confirmed diagnosis of COVID-19 eight weeks before enrollment,\textsuperscript{27} most of whom were asymptomatic or had just mild symptoms. This study demonstrates cardiac inflammation independent of neither the severity of the initial illness nor the overall course of the acute illness. Similar to our study, Xie et al. showed that individuals with COVID-19 infection are at increased risk of cardiovascular complications 30 days after infection, including pericarditis and myocarditis regardless of the need for hospitalization.\textsuperscript{28} Comparable with our study, the study population was tested for the risk of inflammatory heart diseases regardless of previous SRAS-COV-2 vaccination.

Given that SARS-CoV-2 binds to ACE2 to gain host cell entry, there is ongoing debate on whether renin-angiotensinaldosterone system (RAAS) antagonists should be used in COVID-19 patients. Some argued that the blockade might offer clinical benefit,\textsuperscript{54} whereas others queried the possible upregulation of ACE2 as a consequence of such blockades. However, according to the current clinical evidence, the Heart Failure Society of America, the American College of Cardiology, and AHA advise continuing the RAAS antagonist regimen if prescribed for their approved indications, even if the patient contracts COVID-19 later.\textsuperscript{29}
Higher risk of myocarditis and pericarditis was observed in a large population study of recently published by Barda et al. Although both our study and the study by Barda et al. are based on Clalit Health Service patients, there are several important differences between the studies. Barda et al. were focused on COVID-19 vaccination, and thus the matching was designed to neutralize vaccination-related factors, while our study is on a non-vaccinated population. Barda et al. studied the occurrence of myocarditis and pericarditis from positive PCR results up to 42 days, while we study recovering patients starting 10 days after infection and for a significantly more prolonged time. Barda et al.’s analysis also ignores the timing of myocarditis and pericarditis.

Several cases of coronavirus-related myocarditis have been reported. Its pathophysiology likely is a combination of the direct viral insult to cardiomyocytes and the human’s immune response to virally infected myocardium. Simple bedside tests such as serial ECG and cardiac biomarkers can raise suspicion of acute-onset cardiac symptoms. Particular attention should be given to biomarkers changes or trends and not just readings obtained in isolation.

**Conclusion**

Our data suggest that there is no increase in the incidence of myocarditis and pericarditis in COVID-19 recovered patients compared to uninfected matched controls. Further longer-term studies will be needed to estimate the incidence of pericarditis and myocarditis in patients diagnosed with COVID-19.

**References**