Myocarditis in SARS-CoV-2: A Meta-Analysis

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Abstract

There has been a rise in cardiovascular events following the onset of the severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection, a strain that caused COVID-19. Although rare, there has been an increase in reports of myocarditis secondary to both individuals infected from the strain and those who received the COVID-19 mRNA vaccine. The focus of this study is to determine the risk of myocarditis associated with the COVID-19 vaccine and SARS-CoV-2 infection.

Relevant literature was collected from the search engines of PubMed, Google Scholar, and the WHO Global Literature on Coronavirus Disease. Randomized controlled clinical trials and cohort studies reporting the risk of myocarditis induced by SARS-CoV-2 infection and COVID-19 vaccines were used. Meta-analysis was conducted using the inverse variance method using RevMan application software.

Meta-analysis of the compiled data showed a mean risk ratio of 4.74 (95% CI: 2.40 to 9.36; p<0.00001), which indicates there is a significant difference in the risk of COVID-19 induced myocarditis in those with unspecified vaccination status compared to the non-infected population. Meta-analysis of the selected data found a mean risk ratio of 5.01 (95% CI: 4.14 to 6.08; P<0.00001), indicating there is a significant difference in the risk of COVID-19 induced myocarditis between those who are unvaccinated and the non-infected population. Upon meta-analysis of the selected data set, a mean risk ratio of 2.55 (95% CI: 0.84 to 7.74; P=0.10) was found, indicating there is no significant difference in the risk of vaccine-induced myocarditis between those with a vaccinated vaccination status and that of the non-infected population.

The result of this meta-analysis showed infection with SARS-CoV-2 in unvaccinated patients carries a statistically significant increased risk of acquiring myocarditis while those receiving the vaccination do not share this same risk.

Categories: Cardiology, Internal Medicine, Infectious Disease

Keywords: covid-19 vaccine, sars-cov-2 virus, covid-19, vaccine associated myocarditis, covid and myocarditis

Introduction And Background

Introduction

The severe acute respiratory syndrome coronavirus 2, SARS-CoV-2 (COVID-19), is a novel coronavirus that created a worldwide pandemic with over 6.8 million related deaths by the end of 2020 [1]. COVID-19 produces a pneumonia-like illness with symptoms ranging from mild to severe, and possibly even fatal. Serious respiratory outcomes were associated with comorbidities such as COPD, diabetes mellitus and heart failure. The COVID-19 vaccination was developed in hopes of protecting millions of individuals from the new onset effects of this virus. These vaccines sought to develop mRNA spike proteins that could be translated in the cytoplasm, and in turn, create a large number of antibodies to be able to neutralize or destroy the virus.

Myocarditis is a relatively rare inflammatory disease affecting the myocardium caused by a variety of etiologic agents including viruses, toxins, medications, and other inflammatory processes; all of which affect the myocardium leading to heart failure and sudden death in a subgroup of patients. Typically, myocarditis follows viral infection most caused by enteroviruses, specifically Coxsackie group B, and less commonly, adenoviruses, parvovirus B19, hepatitis C, CMV, and HIV. The viruses are thought to infiltrate the myocardium and produce an immunologic activation within the cells causing either cytopathic effect or direct immune damage. It was estimated that about 9 cases per 100,000 patients were seen to develop myocarditis without COVID-19, and about 150 per 100,000 patients were seen to develop myocarditis when infected with COVID-19. Myocarditis in 2020 was seen during inpatient encounters 42% more frequently following the start of the COVID-19 pandemic than it was in 2019. It was estimated that patients with COVID-19 from March 2020 through January 2021, had on average, 15.7 times greater risk of developing myocarditis as compared to those without the COVID-19 infection [2]. It is known that myocarditis was a relatively rare complication prior to the increase in numbers seen following the onset of the COVID-19 pandemic. Although rare in the non-COVID-19 population, the risk of post-COVID myocarditis has been a growing concern with an increased incidence of events in both the unvaccinated and vaccinated population.
Overall, it was recently proposed that unvaccinated patients, regardless of gender, exhibited a higher risk of myocarditis. Interestingly, males aged 12-17 years old were found to have a higher risk of developing myocarditis with the COVID-19 infection. Those who received their second dose of vaccine were also seen to be at an increased risk. Additionally, the risk of myocarditis in unvaccinated 12-17 year old males was found to be 1.8-5.6 times higher [3]. Other sources suggest that there was a seven times increased risk of developing myocarditis in the unvaccinated population versus the vaccinated population with men, once again, being at higher risk [4]. An additional study investigated COVID-19 negative patients who received the vaccine and postulated there may be an increased risk of myocarditis in vaccinated patients aged 18 or older. Of the patients who were vaccinated with one or two doses, 15 resulted in hospital admissions for myocarditis with no previous cardiac history. All patients had an unremarkable hospital stay and did not require readmission [5]. It was of note that younger males were believed to warrant further investigation. Seemingly, myocarditis can be a complication of both COVID-19 and the mRNA vaccine.

Given the recent hesitancy and concern of receiving the COVID-19 vaccine secondary to possible adverse events, such as myocarditis, we have set out to investigate the risk of vaccine induced myocarditis and assess the vaccine’s mitigating effects on acquired myocarditis related to the COVID-19 infection.

Materials and Methods

We included randomized controlled clinical trials and cohort studies that reported the risk of myocarditis induced by the SARS-CoV-2 infection and COVID-19 vaccines. We performed an electronic search on PubMed, Google Scholar, and the WHO Global Literature on Coronavirus Disease relevant articles. The following keyword search terms were used: ["myocarditis" or cardiac disease] AND ["COVID-19" OR "SARS-CoV-2" OR "Coronavirus"]; ["myocarditis" or "cardiac disease"] AND ["COVID-19 Vaccination" OR "SARS-CoV-2 Vaccination OR "Coronavirus Vaccine"]. There were no exclusions based on the size or type of study. There were also no exclusions on sex, age, or race. The study selection process is identified in figure 1. A total of 293 studies were screened, and 12 studies were included in the review, as seen in figure 1. The characteristics of these studies can be found in Table 1. The primary outcome was COVID-19 induced myocarditis in patients with an unknown vaccination status. The secondary outcome was COVID-19 induced myocarditis in unvaccinated patients. The tertiary outcome was COVID-19 vaccine induced myocarditis. The distribution was normalized using standard errors, calculated with the following equation: Standard error: (upper limit - lower limit)/3.92. Meta-analysis was conducted using the inverse variance method using RevMan application software.
<table>
<thead>
<tr>
<th>References</th>
<th>Year of Publication</th>
<th>Country</th>
<th>Risk of Bias</th>
<th>Sample Size</th>
<th>Patients with Myocarditis</th>
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<td>COVID-19 Infection, Unspecified Vaccination Status</td>
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**TABLE 1: Characteristics of studies**

**Review**

**Results**

Coronavirus-Induced Myocarditis in Patients of Unspecified Vaccination Status

All studies were included in this study based on the previously determined exclusion criteria. There was found to be significant heterogeneity (P<0.00001, I²=90%), and therefore, a reverse variance model was utilized for analysis. This heterogeneity may be a consequence of the smaller sample size of the meta-analysis, and therefore, was still considered for analysis. Meta-analysis of the compiled data showed a mean risk ratio of 4.74 (95% CI: 2.40 to 9.36; p<0.00001), which indicates there is a significant difference in relative risk of COVID-19 induced myocarditis in those with an unspecified vaccination status compared to the non-infected population (Figure 2).
FIGURE 2: Forest plot on COVID-induced myocarditis, vaccination status of patient is unspecified.

Coronavirus-Induced Myocarditis in Patients of Unvaccinated Status

No studies were excluded from this meta-analysis based on the exclusion criteria. There was found to be significant heterogeneity ($P = 0.0001$, $I^2 = 86\%$) and therefore, a reverse variance model was used for analysis. Meta-analysis of the selected data found a mean risk ratio of 5.01 ($95\% CI: 4.14 \text{ to } 6.08; P = 0.00001$). This indicates there is a significant difference in risk of COVID-19 induced myocarditis between those who are unvaccinated and the non-infected population (Figure 3).

FIGURE 3: Forest plot on COVID-induced myocarditis in unvaccinated patients.

Coronavirus-Induced Myocarditis in Patients of Vaccinated Status

All studies found upon review of the literature were included based on the determined exclusion criteria. There is some degree of non-significant heterogeneity found ($P = 0.19$, $I^2 = 33\%$), however, a reverse variance model was still utilized. Upon meta-analysis of the selected data set, a mean risk ratio of 2.55 ($95\% CI: 0.84 \text{ to } 7.74; P = 0.10$) was found, which indicates there is no significant difference in the risk of coronavirus-induced myocarditis between those who are vaccinated and that of the non-infected population (Figure 4).

FIGURE 4: Forest plot on COVID vaccine-associated myocarditis.

Discussion

In this meta-analysis, we found there is a significant increase in the relative risk of suffering from SARS-CoV-2-induced myocarditis when there was no confirmation of vaccination (Figure 2 & 3). This is contrasted with the finding that there is no significant increase in risk of this sequelae among those with a confirmed history of COVID-19 vaccination (Figure 4). This further supports previous primary analyses that found the risk of myocarditis associated with exposure to COVID-19 through infection is far greater than that associated with vaccination [12]. A 2022 review article concluded that the incidence of SARS-CoV-2-induced myocarditis is estimated to be approximately 100 times greater than that of COVID-19 vaccine induced myocarditis [16]. This supports the findings found within this analysis and speaks to subsequent conclusions drawn.
It is important to juxtapose the results of this meta-analysis with previous studies that have provided results that directly oppose the conclusions shown here. There have been multiple studies that found there is no significant difference in the rates or risk of SARS-CoV-2-induced myocarditis in individuals without vaccination and that of the non-infected population. One study concluded that many of the cases of SARS-CoV-2-induced myocarditis may be due to Takotsubo cardiomyopathy, clinically indistinguishable from SARS-CoV-2-induced myocarditis. Therefore, it was concluded that one cannot be exclusively assigned to a unifactorial cause [17]. However, the increased prevalence of myocarditis in those infected with SARS-CoV-2 compared to the non-infected population, as demonstrated by this meta-analysis, should indicate that these cases are directly related with SARS-CoV-2, regardless of pathophysiology. Additionally, there is an increasing usage of the Dallas criteria for the confirmation of myocarditis in the setting of both SARS-CoV-2-induced and COVID-19 vaccine induced myocarditis [18]. Dallas criteria states that the diagnosis of myocarditis is dependent on the presence of "inflammatory infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes, not typical of ischemic damage associated with coronary artery disease" [19]. Conversely, the currently accepted diagnostic criteria for Takotsubo cardiomyopathy states that there must be the absence of confirmed or suspicion of underlying myocarditis [20]. When taking these two sets of criteria into consideration, the gray area that has been suggested between SARS-CoV-2-induced myocarditis and Takotsubo cardiomyopathy is more black and white than suggested in the Haussner study.

Additionally, some studies have demonstrated a significantly increased risk of myocarditis in those who received the COVID-19 vaccination compared to that of the general population. This conclusion is also dependent on the demographics of the individuals. One study found there is a significantly increased risk of this sequelae in adolescents compared to adults and in male adolescents compared to their female counterparts [10]. However, current data suggests that this sequelae has an estimated rate of 52.4 to 105.9 cases per million doses administered. Additionally, most cases appeared to be self-limiting with the majority of patients only requiring supportive treatment [21]. Therefore, while this complication exists, it is not only on a much smaller scale than that of the SARS-CoV-2-induced myocarditis, but it is also much milder in symptomatology and prognosis. Additionally, it cannot be definitively concluded that either the result of the Won Lee study or the results of the randomized controlled trials can be generalized to the entire population and even among male adolescents, there is now sufficient data to suggest that the vaccination carries a rare sequelae of myocarditis, and an even rarer risk of serious disease resulting from this sequelae.

Several limitations of this study include the sample size of the data set being analyzed in this meta-analysis, which is also a result of the relative novelty of the subject matter. A limitation specific to meta-analysis is that by combining results from multiple sources, there is an ever present risk of skewing the data set. This can contribute to the overall validity of the study and the conclusions drawn. Additionally, at the height of the COVID-19 pandemic, there were many more sick patients, leading to skewed data. Therefore, all conclusions within this study must be taken in tandem with other available evidence and the original studies being analyzed.

Future directions include the compilation of a more extensive data set to increase the statistical power of the meta-analysis. Additionally, COVID-19 has been associated with a variety of other cardiac and non-cardiac sequelae and therefore, the future inclusion of these other conditions will allow for the better generalization of the protective effect of COVID-19 vaccination.

***Disclaimer: All conclusions drawn from this study do not necessarily represent a definitive answer to the importance of COVID-19 vaccination and therefore no clinical decision should be made based on this preliminary data.

Conclusions

Conclusion

Upon meta-analysis of a compilation of previous studies looking at the incidence and relative risk of SARS-CoV-2-induced myocarditis, it was found there was a significantly higher average risk among those with unspecified vaccine status or those who were unvaccinated compared to the non-infected population. Noting the insignificant difference in acquired myocarditis following infection with COVID-19 between those who are vaccinated, it can be concluded that infection with SARS-CoV-2 in the unvaccinated carries a significant risk of myocarditis, and that the vaccination is protective from this sequelae. These results support the continued COVID-19 mRNA vaccination for all those medically able to receive it.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that no financial support was received from any organization for the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no
other relationships or activities that could appear to have influenced the submitted work.

References