

## Peer Review File

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### Reviewer A

The authors sought to evaluate the incidence of chest pain presentations to the Emergency Department during the pandemic and the corresponding resource utilization.

#### Comment 1:

In the Abstract, I would recommend changing the order of this sentence or perhaps making it two sentences, as it was confusing to read on first glance: "ED chest pain attendance rates and admission rates increased from a median of 0.5% (interquartile range, IQR 0.3 – 0.5) and 26.2% (IQR 24.1 – 29.1) of ED attendances pre-pandemic, to 0.9% (IQR 0.7 – 2.0) during pandemic and 40.9% (37.6 – 56.6) after the mRNA COVID-19 vaccination was introduced (both  $p < 0.001$ ), respectively."

#### Reply 1:

We appreciate the feedback and have amended the sentence for clarity.

Changes in the text (Page 1, Lines 14-18): "Comparing the pre-pandemic period to the period after the mRNA COVID-19 vaccination was introduced, ED chest pain rates increased from a median of 0.5% of ED attendances (interquartile range, IQR 0.3 – 0.5) to 0.9% (IQR 0.7 – 2.0) ( $p < 0.001$ ), while admission rates increased from a median of 26.2% of ED attendances (IQR 24.1 – 29.1) to 40.9% (IQR 37.6 – 56.6) ( $p < 0.001$ )."

#### Comment 2:

I think that a limitation is the practice of the particular institution to admit all patients with chest pain within 1 week of their second vaccine dose. Per my understanding, that would occur in the absence of other signs of myocarditis, just to be cautious. That will certainly impact the admission rates during the pandemic, and it would be worthwhile to mention that as a limitation to the final numbers, since there's variability in this practice among hospitals.

#### Reply 2:

We agree that the increase in admission rates results from our protocol to admit all patients with chest pain within 1 week of their second vaccine dose, and have included this in our discussion.

(Refer Discussion, See Page 12, lines 235-238) In addition, we have added this to the Limitations section, as recommended by the Reviewer.

Changes in the text (Page 12 Lines 249-250): "Our findings reflected local practices, and physician decisions were guided by our institution's COVID-19 protocols."

#### Comment 3:

Of note, the figures were not included in the packet to review unfortunately, but I'm happy to review them.

Reply 3:

We appreciate the feedback. We have attached the tables and figures.

### **Reviewer B**

The authors have made great efforts to evaluate ED attendance due to chest pain in adolescents after introduction of Covid-19 vaccine. However, the manuscript is not providing sufficient data to support the mentioned increased prevalence of myo/pericarditis. Additionally, some information are missing (see below), some statements are contradictory, and a more clear expressing of the dynamic process across the mentioned time periods would be useful.

Some comments:

Comment 1:

-page 2, line 32-39: I suggest results description more clearly . Line 37: that means, only cardiac enzyme orders increased?

Reply 1:

We have edited the phrasing as per reviewers A and B's suggestion. Yes, only cardiac enzyme orders increased.

Changes in text (Page 1 Lines 18-21): "Cardiac enzyme orders among ED visits for chest pain increased from a pre-pandemic median of 0% (IQR 0.0 – 2.6) to a post-vaccination median of 26.1% (IQR 17.2 – 56.2) (p<0.001) and were due to concerns for vaccine-related myocarditis."

Comment 2:

-page 3, line 70: type of mRNA COVID-19 vaccination would be required

Reply 2:

In Singapore, we only had the Pfizer-BioNTech/Comirnaty vaccine available for adolescents 12-18 years old during the study period. We clarified on the type of mRNA COVID-19 vaccination in the Introduction.

Changes in text: (Page 3 lines 37-39): "Only the Pfizer-BioNTech/Comirnaty mRNA vaccine was approved locally for use in adolescents at that time."

Comment 3:

-page 6, line 184: pre-pandemic really no adolescents ever presented with myocarditis and chest pain??

Reply 3:

During the pre-pandemic phase studied, there were no adolescents with an ED or final discharge diagnosis of myocarditis, among those who presented with chest pain. We did have 1 case of pericarditis.

Changes in text (See Page 8, lines 145-146): “During the pre-pandemic phase studied, there were no adolescents with an ED or final inpatient diagnosis of myocarditis, among those who presented with chest pain”

Comment 4:

-page 7, line 186-199: were any more investigations performed in the 7 patients with diagnosed myocarditis? Such as lab. tests, virology, search for other potential causes of myocarditis, MRI?,

Reply 4:

These patients underwent a microbiological workup which returned negative for influenza, Parvovirus, Adenovirus, Enterovirus and Parechovirus. Covid testing was negative, and 6 of 7 patients also had SARS-CoV-2-IgG (N protein) antibody testing done, which were negative. Inpatient MRI was performed for 3 patients.

Changes in text (See Page 8-9, lines 158-166): “All tested negative for COVID-19, and none had documented COVID-19 infection prior to presentation. Six of the 7 patients had SARS-CoV-2 IgG (N-protein) antibody testing done, and all were negative. Microbiological workup for other infective causes of myocarditis in these 7 children returned negative for Influenza A and B, Parvovirus, Adenovirus, Enterovirus and Parechovirus. Three patients underwent cardiac magnetic resonance imaging (MRI) during their inpatient stay. Decision for cardiac MRI was based on individual physician’s discretion. Out of the 3 patients, one had late Gadolinium enhancement in the left ventricle compatible with myocarditis, while 2 had subtle or suspected late Gadolinium enhancement.”

Comment 5:

- line 194: Are there any information available about a) prior COVID infection, b) symptoms direct after vaccination (fever, body aches), c) distance between 1st and 2nd COVID-19 shots?

Reply 5:

a) None of the 7 patients had documented COVID infection prior to their vaccination. 6 of 7 patients had SARS-CoV-2-IgG (N protein) antibody testing done, which were negative.

b) Presenting complaint symptoms are documented in Table 2.

c) Unfortunately, we do not have information regarding the time period between the 1<sup>st</sup> and 2<sup>nd</sup> vaccine dates.

Changes in text (Page 8, lines 158-159): “All tested negative for COVID-19, and none had documented COVID-19 infection prior to presentation.”

We re-attach the tables and figures. Please refer to Table 2.

Comment 6:

- page 8, line 215-220: The authors mention more frequent attendance due to chest pain. Despite that ECG usage remained stable across the three time periods? Is this just explainable by the more frequent ECG use pre-pandemic?

Reply 6:

We thank the Reviewer for this query. In our department, regardless of pre- or post-pandemic, children with chest pain routinely undergo the 12-lead ECG. This is a non-invasive and painless procedure that is routinely ordered by the triage nurses when the child presents with chest pain. The trend of ECG, chest x-ray and cardiac enzymes use is graphically represented in Figure 3.

Changes in text (Page 9, Line 177): “The use of ECG and chest radiographs remained similar across the three time periods (Fig 3).”

Comment 7:

- page 9, line 255-264: this paragraph needs to be shortened

Reply 7:

We have reduced redundancy and shortened the paragraph as advised by the Reviewer.

Changes in text (Page 11, Lines 218-222): “The Children’s Hospital of Philadelphia implemented a clinical pathway for evaluation of paediatric chest pain based on history and physical examination.(14) Post implementation, 3.9% of paediatric chest pain visits had troponin levels performed, 35.6% had chest radiographs, 47.7% had electrocardiograms and 1.2% had echocardiograms performed in the emergency department.”

Comment 8:

- line 271: It became not clear, where are the data for the increased incidence of myocarditis in your study population, what was the myocarditis incidence pre-pandemic and before vaccination? These data should be clarified and statements made more clearly.

Reply 8:

Please refer to Table 1 and Figure 2 for the data showing the increased incidence of myocarditis in our study population.

(Page 8 Lines 145 – 150): “During the pre-pandemic phase studied, there were no adolescents with an ED or final inpatient diagnosis of myocarditis, among those who presented with chest pain. There was 1 case of pericarditis which presented in March 2020. Following the introduction of mRNA COVID-19 vaccination in adolescents in Singapore, 7 cases (6 males and 1 female) of vaccine-related probable myocarditis were diagnosed. (Fig 2) All occurred after the second dose of mRNA COVID-19 vaccination.”

## **Reviewer C**

In this study the authors tried to describe their single center experience about the uptick of children and adolescents presenting with chest pain to their emergency department post COVID19 mRNA vaccination. After reading the manuscript, I feel this is well-written.

Some revisions need to be done:

Comment 1:

1. Page 6 under results section, line 165- its mentioned fig 1 but I did not see any figures in the manuscript.

Reply 1:

We have re-attached the Tables and Figures.

Changes in text:

NA

Comment 2:

2. Page 6, line 167, table 1- There is no table listed in the manuscript that I can see.

Reply 2:

We have re-attached the Tables and Figures.

Changes in text:

NA

Comment 3:

3. Page 7, line 202- In terms of the laboratory investigations, the authors reported that all the patients tested negative for COVID-19. I am curious if they performed COVID-19 Ig G antibodies to see if the patients had COVID-19 infection because MIS- C which is Multisystem Inflammatory Syndrome in Children is a diagnosis which is associated with COVID-19 infection and presents in a similar way with symptoms consistent with chest pain, elevated troponins like in myocarditis. It usually occurs 2-4 weeks after acute COVID-19 infection and sometimes the children can be asymptomatic from the infection and so checking SARS-COV2 Ig G antibodies will help to confirm if the myocarditis is from the COVID-19 infection or vaccine induced. Also to remember that testing negative for COVID -19 does not mean anything as the patient might had the infection and recovered from it already by the time of testing.

There are tests to differentiate the antibodies developed from infection vs vaccine.

It would have been a great study if the authors were able to differentiate the chest pain or the myocarditis symptoms/signs are secondary to recent covid-19 infection and hence a result of MIS-C or it is secondary to mRNA vaccines.

Reply 3:

None of the 7 patients had documented COVID infection prior to their vaccination. 6 of 7 patients had SARS-CoV-2-IgG (N protein) antibody testing done, which were negative.

Changes in text (Page 8, lines 158-160): "All tested negative for COVID-19, and none had documented COVID-19 infection prior to presentation. Six of the 7 patients had SARS-CoV-2 IgG (N-protein) antibody testing done, and all were negative."