

Peer Review File

Article Information: <http://dx.doi.org/10.21037/tp-20-188>.

This is an interesting review study of MIS-C cases published during 2 months between early April and early June 2020.

The main remarks are the following:

A significant number of cases have been published during the last 3 months. A review of only the cases published until June 7 is not very meaningful anymore.

Recent reviews have also been published. This is therefore not a first case review.

Reply: We appreciate your comments and we are sorry that we only included cases before June 17, 2020. The reasons are as follows: (1) We constructed the frame of this article in early June and we spent around one month to finish it. We aimed to provide an overview on this newly emerged disease as soon as possible, considering the emergent situation. (2) We submitted the manuscript in July 10 and at that time it was the first case review on this issue. Since recent reviews have been published, we have modified our wording accordingly. (3) Although the COVID-19 pandemic evolves rapidly, our main conclusions did not change and it would still reflect the clinical picture of MIS-C. Besides, we pointed out that clinical researchers should pay more attention to the reporting quality when conducting a case study, as another and special highlight of our article. Based on the above reasons, we consider that updating the article with new cases won't add much meaning but will take a lot of time. We sincerely hope you could understand.

Changes in the text: Page 15, Line 331. Page 20, Line 427.

It would be interesting to recalculate the percentages of clinical and biological manifestations taking into account each time the number of cases in order to obtain for each item a real prevalence which will be the total sum of the cases. (this gives more relevant information than the range of prevalences, especially when the range is large).

Reply: Thank you for your valuable suggestion. We have recalculated and combined the percentages of clinical manifestations, imaging findings, treatments and outcomes using STATA version 15. Considering the great statistical and clinical heterogeneity of laboratory findings (varied time point in a disease course when recording the results, varied test equipments and that most articles showed their results as medians (range) instead of means (SD)), we haven't combined the values of laboratory findings.

Changes in the text: We have added a column of combined percentages in Table 2, Table 4 and Table 5 and described it in Page 8, Line 173-186.

The discussion should be expanded to emphasize the fact that this syndrome is temporally staggered in relation to acute illness. The significance of a positive PCR

that could be a false positive (identification of viral RNA residues) should be discussed. Immunological mechanisms should be discussed.

Reply: Thank you. We have revised the section accordingly.

Changes in the text: Page 17-18, Line 369-388.

Line 74: We can add that the first alert in the European media dates from April 27th with an article in the Guardian informing the population of 12 cases in England.

Reply: Thank you for your helpful information. We've searched the website of the Guardian but failed to identify the source of this news. We found similar information on tweeter published by Paediatric Critical Care Society on April 27 that described an alert circulated from the U.K. about multi-system inflammatory disease in children with COVID-19.

Changes in the text: Page 4, Line 93.

Line 84: It is useful to mention here the different synonyms of the disease.

Reply: Thank you. We have added several common terms of the disease.

Changes in the text: Page 4-5, Line 105-108.

Line 110: indicate that although the limit for children is 21 years of age, published cases over 20 years of age are exceptional. Research should be extended to young adults to identify these patients.

Reply: Thanks for the information. We have added the sentence as suggested.

Changes in the text: Page 6, Line 138-139.

Lige 142: immunomodulator in the plural

Reply: Thank you. We have replaced "immunomodulator" to "immunomodulators".

Changes in the text: Page 7, Line 167.

Line 146 147: Add the actual percentage recalculated from the data for each item.

Reply: Thank you for your suggestion. We have recalculated the percentage of clinical manifestations, imaging findings, treatments and outcomes.

Changes in the text: Table 2, Table 4 and Table 5.

Line 205: A detailed leukocyte account is required.

Reply: Thank you. We have added the leukocyte, neutrophil and lymphocyte count in this section.

Changes in the text: Page 11, Line 247-249.

Line 226 in total how many angiograms were performed

Reply: The sentence "Myocarditis (43%-100%) and coronary artery dilation (14%-93%) were common" was based on echocardiography instead of angiograms.

No angiograms were reported, except one study that mentioned two patients had outpatient CT coronary angiogram, with no new abnormalities. After rechecking and recalculating the percentages, myocarditis was reported in 61% (95%CI: 29%, 93%)

of patients in three studies and coronary artery dilation in 23% (95%CI: 8%, 39%) of patients in six studies. We have changed the numbers in the section.

Changes in the text: Page 12-13, Line 265-278.

Line 225 specify the difference between coronary dilatation and aneurysm. The identification of 93% coronary dilatation concerns how many patients?

Reply: Both coronary dilatation and aneurysm were detected by heart ultrasound.

Coronary artery dilation was defined if the coronary artery diameter z score was between 2.0 and < 2.5. Aneurysm was defined if the z score was 2.5 or greater. The identification of 93% coronary dilatation was a miscalculation and we've changed the range of coronary dilatation into 2% to 60%. The number 93% referred to 14 out of 15 patients who had coronary artery abnormalities (one coronary aneurysm, six dilation and seven prominent coronary arteries on echocardiogram but normal measurements)

Changes in the text: None.

Line 230: how many patients received hydroxycloquine and/or azithromycin

Reply: Only one study mentioned the use of hydroxycloquine for initial suspicion of systemic lupus erythematosus [Pouletty M et al. Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 mimicking Kawasaki disease (Kawa-COVID-19): a multicentre cohort. Annals of the rheumatic diseases 2020]. Use of azithromycin was not mentioned. Two studies noted that 86% to 100% of patients received broad-spectrum antibiotics, commonly third generation cephalosporin.

Changes in the text: None.

Line 274 this is not the first review published of several recent case reviews

Reply: Sorry about this. We've explained this in Reply 1 and changed our wording accordingly.

Changes in the text: Page 15, Line 331. Page 20, Line 427.

Line 523 table 2. Add a column with the recalculated frequencies

Reply: Thank you. We've added a column of the recalculated frequencies.

Changes in the text: Table 2, Table 4 and Table 5.

Line 528 add eosinophilia

Reply: Sorry, we are not sure if you mean eosinophilia here, because there were no elevated eosinophils reported in our study.

Changes in the text: None.