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OPEN PEER REVIEW

Comparison of Clinical Features and Outcomes of Shocks in Multisystem Inflammatory Syndrome in Children Associated with COVID-19 (MIS-C), Septic Shock, and Cardiogenic Shock

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1 Original submission

1 comment · 24 Mar 2024

Kosar Asna Ashari Reviewer

MINOR REVISION 24 Mar 2024

"Comparison Clinical Features and Outcome of Shocks in Multisystem Inflammatory Syndrome in Children Associated with COVID-19 (MIS-C), Septic Shock and Cardiogenic Shock" compares characteristics of 60 patients in three groups: MIS-C, septic shock, and cardiogenic shock. The findings are invaluable as the different approaches to treatment are lifesaving. There are a few notes I need to mention:

1. The criteria for MIS-C, although referenced, need to be mentioned. The criteria for cardiogenic shock also need to be mentioned. The reader would wonder in the first place if these criteria overlap. A table showing these three sets of criteria side by side would be helpful.
2. The discussion can benefit from comparison of the findings of the study with those in the literature. The treatment approaches can be further discussed.
3. There is debate about whether septic shock and/or MIS-C can lead to cardiogenic shock. This can be addressed and explained in relation to the patients in the study. Clarifying the inclusion criteria also helps.
4. The manuscript needs minor English language revision.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Reply to reviewers

Reviewer 1	
1.Please more declare in table 1, about the neurologic and hematologic manifestations.	Hematological presentation is petechiae. Neurological presentation is seizure
2.the result of interpretation of inflammatory parameter such as ferritin, CRP and ESR, because the number of cardiogenic shock and septic shock were lower than the MISC shock and if there were more, it would be more valuable.	The pathophysiology of MIS-C shock is thought to be attributable to a hyperimmune response. Meanwhile, cardiogenic shock and septic shock involve hemodynamic and circulatory disturbances, triggering systemic inflammation and organ dysfunction. According to the pathophysiology, the inflammatory markers may elevate in those groups. However, in this study, the number of cardiogenic shock and septic shock groups were lower than the MIS-C shock. It might affect the interpretation of inflammatory parameters. Therefore, if sample size increased, it would be more valuable.
3. Please more compare the result of lymphopenia and cardiac involved in MISC patients with other references.	In term of lymphocyte count, we found that the MIS-C shock group had a significant lymphopenia compared with the other groups. This result is in line with previous study and demonstrated that low lymphocyte count was significantly associated with contractility dysfunction in MIS-C Reference:

	- Ludwikowska KM, Moksud N, Tracewski P, Sokolski M, Szenborn L. Cardiac Involvement in Patients with Multisystem Inflammatory Syndrome in Children (MIS-C) in Poland. Biomedicines 2023; 11(5): 1251.

Reviewer 2	
1.The criteria for MISC, although referenced, needs to be mentioned. The criteria for cardiogenic shock also needs to be mentioned. The reader would wonder in the first place if these criteria overlap. A table to show these three side by side would be helping.	The diagnostic criteria for MIS-C were based on the Center of Disease Control and Prevention (CDC) definition [13]: 1) fever ≥ 38°c or subjective for ≥ 24 hours, 2) laboratory inflammation (C-reactive protein, erythrocyte sedimentation rate, fibrinogen, D-dimer, ferritin, LDH, interleukin-6, neutrophilia, and hypoalbuminemia), 3) severe illness requires hospitalization, 4) ≥ 2 organ systems involved (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic, and neurologic), 5) no other plausible diagnosis, 6) SARS-CoV-2 infection or exposure (positive PCR serology or antigen test, COVID-19 exposure within 4 weeks before onset). The diagnosis of cardiogenic shock was defined as: 1) clinical signs (tachycardia, dyspnea, jugular vein distention, and hepatomegaly) 2) evidence of myocardial dysfunction by echocardiograph Reference: - Center for Disease Control and Prevention. Information for healthcare providers about multisystem inflammatory syndrome in children (MIS-C). Available from https://www.cdc.gov/mis/mis-c/hcp/

	index.html - Wheeler DS, Basu RK. Pediatric Shock: An Overview. The Open Pediatric Medicine Journal 2013;7:2-9. - Brissaud O, Botte A, Cambonie G, Dauger S, Blanquat LDS, Durand P, et al. Experts' recommendations for the management of cardiogenic shock in children. Ann Intensive Care 2016;6:14.
2. The discussion can benefit from comparison of the findings of the study with those in literature. The approaches of treatment can be further discussed.	Intravenous immunoglobulin (IVIG) and glucocorticoids are the most commonly used as immunomodulatory medications in MIS-C. The American College of Rheumatology recommends using IVIG in combination with glucocorticoids as first-tier therapy for hospitalized children with MIS-C. The Thai guidelines recommend treating MIS-C shock with intravenous immune globulin 2 g/kg and pulse methylprednisolone. Additionally, Low-dose aspirin should be used in patients with MIS-C and continued until the platelet count is normalized and normal coronary arteries are confirmed at >4 weeks after diagnosis. In this study, we observed that all MIS-C shock patients received glucocorticoids, IVIG, and antiplatelet therapy. Notably, there were

	no reported fatalities in the MIS-C shock group. Interestingly, the previous study showed using a different dose of IVIG and steroids in MIS-C patients, 63.8% received IVIG at the dose of 1 g/kg, and 36.2% received at the dose of 2 g/kg. The results indicated good outcomes as all patients had a proper response, no cardiac complications, and a low mortality rate. Therefore, they concluded that IVIG at the dose of 1 g/kg might be enough for treatment. The future research should further investigate the optimal dose of immunomodulatory medications in MIS-C. and MIS-C shock Reference: - Henderson LA, Canna SW, Friedman KG, M Gorelik, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV-2 and Hyperinflammation in Pediatric COVID-19: Version 3. Arthritis Rheumatol 2022; 74(4): e1–e20. - Sedighi I, Karimi K, Sedighi P, Tanasan A, Shalchi Z, Molaei F, et al. Clinical and Laboratory Patterns

	of Multisystem Inflammatory Syndrome in Children Related to Coronavirus Disease 2019 in the West of Iran. Iran J Pediatr 2022;32(1):e119041.

Reviewer 3	
1.The authors could improve the discussion by providing more contextualization and interpretation of their findings in relation to existing literature.	A similar previous study reported that the median age of patients was 7 years and fever, rash, and abdominal pain were the most common clinical presentations Reference: - Mamishi S, Movahedi Z, Mohammadi M, Ziaee V, Khodabandeh M, Abdolsalehi MR, et al. Multisystem inflammatory syndrome associated with SARS-CoV-2 infection in 45 children: A first report from Iran. Epidemiol Infect. 2020;148. e196. According to this study, poor left ventricular dysfunction was the most common cardiac finding. Similarly, several studies showed left ventricular systolic and diastolic dysfunction were present in MIS-C patients in the acute phase of the disease Reference: - Kavurt,corresponding AV, Bağrul D, Gül AEK, Özdemiroğlu N, Ece İ, Çetin İİ, et al. Echocardiographic Findings and Correlation with Laboratory Values in Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-1. 9Pediatr Cardiol 2022; 43(2): 413–425.

	- Matsubara D, Kauffman HL, Wang Y, Calderon-Anyosa R, Nadaraj S, Elias MD, et al. Echocardiographic findings in pediatric multisystem inflammatory syndrome associated with COVID-19 in the United States. J Am Coll Cardiol 2020;76(17):1947–1961. - Karim A, Ghafourii P, Alilou S, Rezaei N, Talesh SA, Ashraf H. Echocardiographic Findings in Multisystem Inflammatory Syndrome in Children (MIS-C) Associated with COVID-19: A Systematic Review. Iran J Pediatr 2022;32(2):e119001.
2. A more detailed discussion on the pathophysiological mechanisms underlying the observed differences in MIS-C shock would enhance the clinical relevance of the study.	In the case series report, MIS-C shock appeared to be a combination of distributive and cardiac dysfunction. Exaggerated immune response and hyperinflammation state possibly affect the endothelium of vessels and the myocardium, leading to vasodilatory and ventricular dysfunction Reference: - Caro-Patón GL, Azagra-Garde AM, García-Salido A, Cabrero-Hernández M, Tamariz A, Nieto-Moro M. Shock and Myocardial Injury in Children With Multisystem

	Inflammatory Syndrome Associated With SARS-CoV-2 Infection: What We Know. Case Series and Review of the Literature. J Intensive Care Med 2021;36(4):392-403
3. The role of glucocorticoids in the management of MIS-c is very important. The authors should consider discussing the management strategies and treatment of MIS-C shock with glucocorticoids, intravenous immunoglobulin. Relative protocol and study	Intravenous immunoglobulin and glucocorticoids are the most commonly used as immunomodulatory medications in MIS-C. The American College of Rheumatology recommends using IVIG in combination with glucocorticoids as first-tier therapy for hospitalized children with MIS-C []. The Thai guidelines recommend treating MIS-C shock with intravenous immune globulin 2 g/kg and pulse methylprednisolone. Additionally, Low-dose aspirin should be used in patients with MIS-C and continued until the platelet count is normalized and normal coronary arteries are confirmed at >4 weeks after diagnosis. Reference: - Henderson LA, Canna SW, Friedman KG, M Gorelik, Lapidus SK, Bassiri H, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV-2 and Hyperinflammation in

	Pediatric COVID-19: Version 3. Arthritis Rheumatol 2022; 74(4): e1–e20. -
4. Addressing the study's limitations more comprehensively, including potential biases and confounding factors, would strengthen the discussion.	Fourthly, there is a risk of selection bias in our study because we selected patients from medical records. Finally, inter-observer variability in reporting the results of echocardiographic and USCOM findings, we could not conduct statistical analysis.
5.For the background on MIS-C, incorporating a few more of the latest high-impact studies/reviews from 2022 or 2023 could further strengthen the literature coverage.	The recent study demonstrated that the mean age was 9 years and fever, rash, and gastrointestinal symptoms were common presentations In the multicenter study, there was a higher proportion of hospitalizations with shock in MIS-C compared with KD Reference: - Santos MO, Gonçalves LC, Silva PAN, Moreira ALE, CRM Ito, Peixoto FAO, et al. Multisystem inflammatory syndrome (MIS-C): a systematic review and meta-analysis of clinical characteristics, treatment, and outcomes. J Pediatr (Rio J) 2022;98(4):338-349. - Molloy MJ, Auger KA, Hall M, Shah SS, Schondelmeyer AC, Parikh K, et al. Epidemiology and Severity of Illness of MIS-C and

	Kawasaki Disease During the COVID-19 Pandemic. Pediatrics 2023 ;152(5):e2023062101.
6.For general pediatric shock management, citing a couple of the latest guidelines or expert recommendations could make the references more current.	Early recognition, timely intervention, and close monitoring can improve the outcomes of shock. Hemodynamic monitoring and assessment of fluid responsiveness using dynamic parameters are important to the management of shock Reference: - Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. Pediatr Crit Care Med 2020;21(2):e52-e106. - Gupta S, Sankarcorresponding J. Advances in Shock Management and Fluid Resuscitation in Children. Indian J Pediatr 2023; 90(3): 280–288.

7. If available, more recent literature specifically examining USCOM use in MIS-C or comparing it across shock types could enhance the discussion around hemodynamic findings.	We cannot search for literature about USCOM use in MIS-C because our study is the first investigation of USCOM outcomes in patients with MIS-C shock.

2 Revision 1

0 comments

No public comments in this round.