

Article information: <https://dx.doi.org/10.21037/tp-23-41>

Review Comments-reviewer A

The paper titled “The upregulation of peripheral blood polyamine metabolites spermidine and spermine in children with hand, foot, mouth disease is related to enterovirus 71 capsid protein VP1, but not VP4” is interesting. The results suggest that EV71 capsid protein may regulate the polyamine metabolic pathways of infected cells in a variety of ways. This study provides insights into the mechanism of EV71 infection and polyamine metabolism and has good reference value for the development of EV71 vaccine. However, there are several minor issues that if addressed would significantly improve the manuscript.

Comment 1: There have been many studies on hand, foot, mouth disease. What is the difference between this study and previous studies? What is the innovation? These need to be described in the introduction.

Reply 1: We have modified our text as advised (see Page 5, line 125)

Comment 2: For other human viral infections, how to control the targeted polyamine metabolic pathway? Please give some examples.

Reply 2: We have modified our text as advised (see Page 5, line 114)

Comment 3: It is suggested to increase the sample size or in vitro experiment to evaluate the function of polyamines.

Reply 3: We have modified our text as advised (see Page 14, line 358)

Comment 4: What role does VP1 play in the pathogenesis of EV71 disease and its neurological complications? It is suggested to add relevant contents.

Reply 4: We have modified our text as advised (see Page 4, line 92)

Comment 5: The introduction part of this paper is not comprehensive enough, and the similar papers have not been cited, such as “Clinical characteristics of 68 children with atypical hand, foot, and mouth disease caused by coxsackievirus A6: a single-center retrospective analysis, PMID: 36247893”. It is recommended to quote the article.

Reply 5: We have modified our text as advised (see Page 4, line 80)

Comment 6: How to provide candidate targets for the treatment of hand, foot, mouth disease based on the results of this study? It is recommended to include relevant descriptions in the discussion.

Reply 6: We have modified our text as advised (see Page 14, line 362)

Review Comments-reviewer B

1. MDAR checklist: Please DO NOT make any revisions to left row in the checklist, you just need to report in the right row. Please kindly re-fill the attached checklist.

Antibodies	Yes (indicate where provided: page no/section/legend)	n/a
For commercial reagents, provide supplier name, catalogue number and RRID, if available.		
Cell materials	Yes (indicate where provided: page no/section/legend)	n/a
Cell lines: Provide species information, strain. Provide accession number in repository OR supplier name, catalog number, clone number, OR RRID		
Primary cultures: Provide species, strain, sex of origin, genetic modification status.		
Experimental animals	Yes (indicate where provided: page no/section/legend)	n/a
Laboratory animals: Provide species, strain, sex, age, genetic modification status. Provide accession number in repository OR supplier name, catalog number, clone number, OR RRID		
Animal observed in or captured from the field: Provide species, sex and age where possible		
Model organisms: Provide Accession number in repository (where relevant) OR RRID		
Plants and microbes	Yes (indicate where provided: page no/section/legend)	n/a
Plants: provide species and strain, unique accession number if available, and source (including location for collected wild specimens)		
Microbes: provide species and strain, unique accession number if available, and source		

Reply: We have modified our text in MDAR checklist.

Besides, there're patients included in your study, please do not fill "N/A" for below items.

Ethics	Yes (indicate where provided: section/paragraph)	
Studies involving human participants: State details of authority granting ethics approval (IRB or equivalent committee(s), provide reference number for approval.	N/A (no involving human participants)	
Human research participants	Yes (indicate where provided: section/paragraph)	n/a
Identify authority granting ethics approval (IRB or equivalent committee(s), provide reference number for approval.	N/A (The study was approved by the Internal Review and Ethics Boards of Guangdong Medical University, Guangzhou First People's Hospital, Guangzhou Nansha Center for Disease Control and Prevention, and Dongguan Dalang Hospital)	
Provide statement confirming informed consent obtained from study participants.	Yes (Materials and Methods/Ethics statement:134)	
Report on age and sex for all study participants.	Yes (Table 1 The demographic and clinical characteristics)	

2. We need two points for this item, please clarify "what is known" and "what is new" respectively.

84 **What is known and what is new?**

85 Polyamines are compounds that are ubiquitous in mammalian cells and play a key role in
 86 various cellular processes. Several studies have shown that targeting polyamine metabolic
 87 pathways can reduce infections caused by viruses. However, the significance of polyamine
 88 metabolites, such as SPD and SPM, in EV71 infection remains largely unknown.

Reply: We have modified our text as advised (see Page 3, line 84)

3. Please structure your Main Text as: **Introduction, Methods, Results, Discussion, Conclusion**. Please add “Conclusion” section for your manuscript.
 Reply: We have modified our text as advised (see Page 14, line 414)

4. Please define ALL abbreviations in Table 1 footnote.

Table 1 The demographic and clinical characteristics

Groups	EV71(n=25)	Un-EV71 (n=57)	HV(n=70)
Female/male	11/14	24/33	34/36
Age (years), mean \pm SD	3.61 \pm 1.48	2.34 \pm 1.29	3.52 \pm 1.08
Maximum body temperature ($^{\circ}$ C), mean \pm SD	39.11 \pm 0.73	39.01 \pm 0.70	-

Reply: We have modified our text as advised in table 1 footnote.

5. Please define all abbreviations in Figure 8 legends. Like SPD, SPM, EV, ORN, etc.

Reply: We have modified our text as advised in Figure 8 legends.