Peer Review File

Reviewer A

First of all, my major concern for this study is the problematic rationale and conclusion of this study. The authors did not use PCT to identify HFMD; they only compared the PCT levels in severe vs. mild HFMD, so the title is misleading. The conclusion focused on the early identification of severe HFMD, however, this is not practical since the severity of HFMD is dynamic and the authors did not investigate the longitudinal changes in PCT along with the changes in the severity of HFMD. Please clearly indicate the clinical research design in the title such as the comparisons of PCT and age between mild and severe HFMD.
Reply: I have modified the text as advised (See page 1, line 2)

Second, the abstract did not explain why the authors focused on these biomarkers and why these biomarkers are potentially associated with severe HFMD in the background, did not describe the inclusion of the subjects, the assessment of clinical factors and biomarkers, and how these outcomes were statistically compared in the methods, did not report the comparability of the two groups and quantify the findings on outcomes of the two groups such as mean and SD in the results, and the conclusion was not made strictly based on the current findings.
Reply: I have modified the text as advised and add some data (See page 1, line 20-29, and table 1-4)

Third, in the introduction of the main text, the authors need to review what has been known on the clinical factors and biomarkers associated with severe HFMD, have comments on the limitations of prior studies and the potential clinical significance of this comparative study, and explain the knowledge gaps to be filled by this study.
Reply: I have modified the text as advised (See page 3, line 9-12)

Fourth, in the methodology of the main text, the methodology of the main text needs to describe the clinical research design, sample size estimation, and assessment of clinical factors. The statistics cannot be simple like this. Please first test the comparability of the clinical characteristics of the two groups, describe the statistical methods for comparing the outcomes between the two groups, and when the baseline is not comparable, please describe the multiple regression analysis to adjust for the baseline confounders. The $P<0.05$ should be two-sided.
Reply: I have modified the text as advised and add some data (See page 4, line39-43)

Reviewer B

The paper titled "Procalcitonin levels in identifying severe hand, foot, and mouth disease" is interesting. Age and blood PCT levels play a vital role in the early identification of severe HFMD. However, there are several minor issues that if addressed would significantly improve

the manuscript.

In the introduction of the manuscript, it is necessary to clearly indicate the value of PCT in evaluating clinical outcomes in patients with blood infection.

I have modified the text as advised (See page 3, line 9-11)

There have been many studies on HFMD. What is the difference between this study and previous studies? What is the innovation? These need to be described in the introduction.

I have modified the text as advised (See page 3, line 13-15)

The research content of this study is too limited, and it is recommended to increase the analysis of polyamine metabolites in peripheral blood of children with HFMD.

Due to time and financial constraints, polyamine metabolite analysis was not performed. (No changes in the text)

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.

I have added the recommended literature. (See page 2, line 52-54)

What is the guiding significance of this study for the use of antibiotics in children with severe HFMD? It is recommended to add relevant content to the discussion.

I have modified the text as advised. (See page 7, line 1-2)

There are many uncertainties in retrospective research, which increase the deviation of research results. How to explain and solve this problem?

I have modified the text as advised (See page 7, line 34)

The number of patient samples in this study is too small, and a large sample study should be added for verification.

It is difficult to increase the sample size. (No changes in the text)

<mark>Reviewer C</mark>

1. References/Citations

Please double-check if more studies should be cited as you mentioned "studies". OR use "study" rather than "studies".

188	that the susceptibility and severity of HFMD are associated with age (14). Moreover,	
189	other studies have demonstrated that BNP and PCT levels can be an indicator of severe	
190	fatal HFMD. Although the pathogenesis of HFMD has not yet been fully clarified (15),	
191	it is related to the inhibition of immune function, especially cellular inhibition of	

217	Studies have also suggested that cellular and humoral immunity are activated after	
218	enterovirus infection, contributing to immune surveillance, response, self-stabilization,	
219	and defense against viral infection (19). T-lymphocyte subsets are an important part of	

I have revised, please see line 178 and 206.

2. Table 1

Please add the description to the table footnote that how the data are presented in table.

WBC count (×10^9/L), mean	14.48±0.80	14.54±0.63
CRP (mg/L), mean	21.14±3.29	19.82±2.10
BNP (ng/mL), mean	389.31±41.42	546.18±53.42
PCT (ng/mL), mean	0.346±0.061	0.568±0.067
ALT (IU/L), mean	18.763±1.67	18.579±0.754
AST (IU/L), mean	20.38±1.85	20.06±1.30

I have revised, please see table1.

3. Table 2-4

Please add the description to the table footnote that how the data are presented in table.

Lymphocyte subsets (%)	Mild group (N=76)	Severe group (N=107)
CD3$^+$CD8$^+$	22.534±0.724	20.685±0.566
CD3$^+$	62.755±1.15	61.166±0.74
CD3$^+$CD4$^+$	43.064±5.683	36.728±0.645

I have revised, please see table 2-4.

4. Table 3

As there is no symbol "*" in the table, please delete the explanation.

*, statistically significant values (P<0.05). WBC, white blood cell; CR
procalcitonin; ALT, alanine aminotransferase; AST, aspartate aminotrai

I have delete.