Peer Review File

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Reviewer A

The article entitled The predicting value of cytokines for the organ injury in the critically ill patients is a reasonable attempt to examine cytokine levels in different acute organ dysfunction subgroups in pediatric ICU patients. Several aspects of the manuscript must be addressed prior to publication.

1. The manuscript requires English editing for grammar and understandability.
Response: we have edited the manuscript for grammar as advised.

2. Figure 1 does not add significantly to the manuscript
Response: Figure 1 is the flow chart of this study (see Page 6, line 127)

3. The authors report that they used the lower level of detection for any levels below the reported level for the assay. Figure 2 shows levels below this and must be clarified. Further, the use of the mann-whitney U test is significantly biased by the undetectable levels. A better method of analysis for these values to be to use a log transformation followed by standard T test to assess differences.
Response: we have modified the analysis methods and figures. (Methods section, see Page 6, line 112-116). We also talked about the limitations of these results in the discussion section (Discussion section, see Page 10, line 241-243).

4. The incidence of acute gastrointestinal injury seems very high and I do not understand what this is – it should be clarified.
Response: The presence of gastrointestinal peristalsis disorders, gastric retention, diarrhea and vomiting, gastrointestinal bleeding is defined as acute gastrointestinal injury. Studies have shown that the incidence of AGI in critically ill adults is more than 70%.
Reference: Chinese Abdominal Intensive Care Association ASfEaCCM. Expert consensus on enteral nutrition for gastrointestinal dysfunction in critically ill patients. Chin J Dig Surg. 2021.

5. Further, the method of defining all of the types of injury should be defined.
Response: The criteria for organ injury were based on international guidelines and/or the criteria from other studies (13-25), which were stated in the manuscript.
References:
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6. Figure 3 does not show IL17A as far as I can tell and this must be clarified.
Response: Thanks for your reminding, we have added IL-17A in Figure 3B.

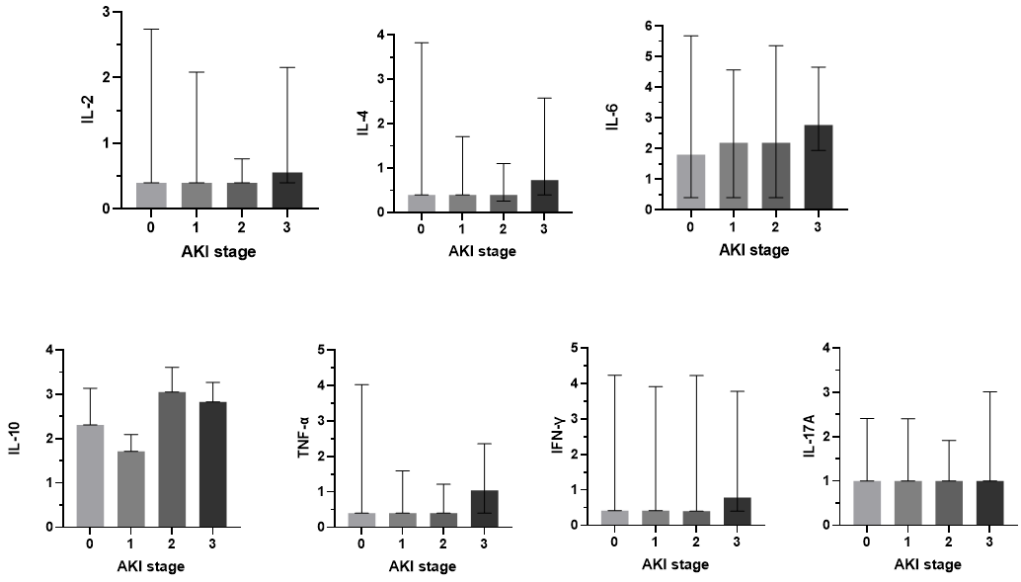
Reviewer B

1. How is end organ disease defined? I'm not sure that I understood this.
Response: Did you mean how to define the organ injury? The criteria for organ injury were based on international guidelines and/or the criteria from other studies. (13-25) (see Page 6, line 101-102)

2. "Heart arrest" needs to be revised to "Cardiac Arrest"
Response: we have modified it as advised.

3. I think this is an interesting topic but there are several dimensions that need to be explored.
What is the temporal relationship between cytokines and development of end organ injury?
Response: The temporal relationship between cytokines and the development of end organ injury is complex and multifactorial. Cytokines, which are signaling molecules of the immune system, play a crucial role in the inflammatory response that can lead to end organ injury. In many cases, the release of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) precedes the development of end organ injury. These cytokines can trigger a cascade of inflammatory responses that contribute to tissue damage and dysfunction in various organs. However, the relationship is not always linear, as the release of anti-inflammatory cytokines and the overall balance between pro-inflammatory and anti-inflammatory factors also influence the development and progression of end organ injury. Additionally, individual variations in immune response, underlying conditions, and the specific context of the disease or injury can all impact the temporal relationship between cytokine levels and end organ damage.

4. Is there a quantitative relationship between cytokine amount and organ injury?
Response: we try to analyze the relation between cytokines and AKI stage, but form the following figures, quantitative relationship between them is not observed.



5. A sub group analysis of cytokines for patients with underlying immunocompromise should be performed. There is literature that cytokine responses are different in these patients.

Response: Thanks for you advice, we made a subgroup analysis of cytokines with/without underlying immunocompromise (see following table). No significant difference is observed in our study group, which may be due to the small sample size.

	Critical group(median)			Control group(median)			Cohort(Critical+Control) (median)		
	Imm	non-imm	p	Imm	non-imm	p	Imm	non-imm	p
IL-2	2.5	2.5	0.167	2.5	2.5	0.245	2.5	2.5	0.277
IL-4	2.5	2.5	0.133	2.5	2.5	0.183	2.5	2.5	0.181
IL-6	456.15	62.2	0.573	2.5	2.5	0.228	43.4	37.2	0.464
IL-10	18.35	13.35	0.222	2.5	2.5	0.062	9.9	10.5	0.144
TNFα	2.5	2.5	0.15	2.5	2.5	0.454	2.5	2.5	0.198
IFNγ	13.95	2.5	0.061	2.5	2.5	0.062	2.5	2.5	0.163
IL-17A	10	10	0.493	2.5	10	0.479	10	10	0.387

Immuno, immunocompromise; non-imuno, immunocompromise.