

Review Form 1.6

Journal Name:	Asian Hematology Research Journal
Manuscript Number:	Ms_AHRJ_92913
Title of the Manuscript:	Observational study on dual marker of T cell activation for early diagnosis of HLH on peripheral blood
Type of the Article	Method Article

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty**', provided the manuscript is scientifically robust and technically sound. To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

(<https://www.journalahrj.com/index.php/AHRJ/editorial-policy>)

PART 1: Review Comments

	Reviewer's comment	Author's comment (if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)
<u>Compulsory</u> REVISION comments	<p>The critical problem of this study is the absence of a definition of HLH. The traditional criteria using the HLH-2004 criteria should have been used to select the patients to be included. Two major clinical criteria for the diagnosis of HLH are fever and splenomegaly.</p> <p>The authors failed to mention the presence of these major clinical features in the 22 patients selected. In fact, only one of the 22 patients was said to have hepatosplenomegaly.</p> <p>How were these 22 patients selected?</p> <p>They should also mention if the patients were consecutively selected for this study or if a certain criterion was chosen for study selection.</p> <p>I suggest that the authors make a table showing which 5 of the eight criteria (fever, splenomegaly, cytopenias, hyperferritinemia, hypertriglyceridemia or Hypofibrinogenemia, Hemophagocytosis, Low or absent NK-cell activity, or Elevation of sCD25 (sIL-2 receptor) >2400 U/ml) each of these 22 patients fulfilled. In addition, it would be highly desirable to describe the genetic origin of this syndrome, if performed demonstrating the presence or absence of genes thus far described including mutations in PRF1, UNC13D, STXBP2, RAB27A, STX11, SH2D1A or BIRC4 (Rafał Machowicz, Gritta Janka and Wiesław Wiktor-Jedrzejczak. Similar but not the same: Differential diagnosis of HLH and sepsis. Critical Reviews in Oncology and Hematology, 2017;114:1-12).</p> <p>In all patients, soluble CD25 level was low in this study which is in contrast to the high level we observe in typical HLH cases, and often in sepsis as well.</p> <p>Only half of the patients had anemia which is again uncharacteristic of HLH. Although extremely high serum ferritin (> 10,000) is almost diagnostic of HLH, it is elevated in other disorders including sepsis, bacterial infection, and autoimmune disease. The authors failed to mention the actual ferritin values of each patient. The mean CRP value of 153mg/L is quite high, and the value tends to suggest an infection (sepsis) and/or autoimmune disease rather than HLH (see the above article I cited).</p> <p>The article the authors cited (ref 16) is the study results of children (up to age 18) who all met HLH-2004 criteria or sepsis criteria. In this particular population, within the CD8+ population, CD38high/HLA DR+ cells > 7% had sensitivity of 1.0 and specificity of 0.89. On the other hand, this current study mentioned nothing about the subjects meeting the HLH2004 criteria, and it appears that most subjects were adult patients.</p>	
<u>Minor</u> REVISION comments		
<u>Optional/General</u> comments	<p>The paper failed to show that the subjects met the diagnostic criteria of HLH. Therefore, the study results they described cannot be interpreted. I would strongly recommend that they construct a table that lists all 22 subjects with positive findings that meet the HLH-2004 criteria. Then they should describe which and how many patients met the criteria CD38high/HLA -DR+ that was reported in the article they referenced (ref 16).</p>	

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PART 2:

	Reviewer's comment	Author's comment <i>(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)</i>
Are there ethical issues in this manuscript?	<i>(If yes, Kindly please write down the ethical issues here in details)</i>	

Reviewer Details:

Name:	Susumu Inoue
Department, University & Country	Michigan State University College of Human Medicine, USA