Author’s response to reviews

Title: MACROPHAGE ACTIVATION-LIKE SYNDROME: AN IMMUNOLOGICAL ENTITY ASSOCIATED WITH RAPID PROGRESSION TO DEATH IN SEPSIS

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Reviewer #2

• I have to repeat... it is incorrect what authors did in the case of MALS definition....the most important: the evaluation of 9 parameters is not the same as the evaluation of 8 characters.....p.8

Reply: We do agree with this reviewer that a scoring system that is using eight parameters can never be the same as a scoring system that is using nine parameters. To adjust for this limitation, allow us expand our rationale.

According to the publication by Fardet et al [1], the original HScore could vary between 0 and 337. The best cutoff value for HScore was 169, corresponding to a sensitivity of 93%, a specificity of 86%, and accurate classification of 90% of the patients. Since bone marrow aspiration providing 35 points, was not available in our sepsis patients, the modified HScore used could vary between 0 and 302. The ambiguity resulting from this modification applies only to patients with a modified HScore varying between 134 and 169. Patients with a modified HScore less than 134 would still not be classified as MALS even if they presumably might score 35 points in the bone marrow aspiration criterion. In a similar reasoning, patients with a modified HScore greater than 169 would still be considered as MALS even if they scored zero in the bone marrow aspiration criterion.

Among the values of the unmodified HS score in our sepsis patients, there were only 144 patients at the “grey zone” between 134 and 169 representing only 2.8% of the total patients i.e. more than 90% of patients were successfully classified even if the bone marrow criterion was missing. Furthermore, in the original HScore the cutoff value of 169 represents the median of the HScore. This is practically a universal scenario: scoring systems that derive from logistic regression analyses provide cutoff values (with the best tradeoff between sensitivity and specificity) that are equal to or very near the median value. Of course, from the clinical point of view the cutoffs may be moved up or down, depending on whether we want to achieve higher sensitivity or specificity. Reverting to the modification of the HScore that was used in the present study, it seems logical to follow the general rule and take the median of 151 as the cutoff value. The reviewer is right in pointing out that the 8-criteria are not the same as the 9-criteria. However, the above line of reasoning provides evidence that the modified 8-criteria HScore are equivalent to the original 9-criteria HScore. To adjust for this limitation and become even more conservative, in our study patients who met the definitions of both HBD and DIC, as suggested by Shakoory et al [2] were also classified as MALS.
A summary of the above rationale is now provided on pg8, ln19-22 and pg9, ln9-18 of the revised manuscript. Moreover, the revised manuscript reads on pg11, ln10-15 and on pg11, ln17-23 an analysis showing that the risk of misclassification using both the modification of the HScore and the presence of both HBD and DIC was at the level of 1.2%. The manuscript now reads on pg11, ln10-15: “In the test cohort, 128 (3.7%) patients were classified with MALS. This classification was due to HScore >151 in 67 patients, to the presence of HBD and DIC in 40 patients and to the co-presence of HScore >151 and HBD and DIC in 21 patients. In total 49 patients had HScore between 151 and 168, eight of whom had also both HBD and DIC i.e. 41 patients of the test cohort (1.2%) had a risk of misclassification” and on pg11, ln17-23: “This classification was due to HScore >151 in 44 patients, to the presence of HBD and DIC in 19 patients and to the co-presence of HScore >151 and HBD and DIC in 10 patients. In total 22 patients had HScore between 151 and 168, four of whom had also both HBD and DIC i.e. 18 patients of the test cohort (1.1%) had a risk of misclassification. This risk could be well-accepted taking into consideration that the original HScore classified correctly 90% of patients [15].”

The lack of data of bone marrow aspiration is also recognized as a limitation of our study on pg14, ln2-4 of the revised manuscript.

References
