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The authors' comments on the letter by Sabour

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We thank Dr. Sabour for his interest in our study and appreciate the opportunity to address his comments [1]. This retrospective study for patients after receiving allogeneic hematopoietic cell transplant (allo-HCT) was undertaken with the following three aims [2]: (1) to examine the diagnostic value of serum ferritin for hemophagocytic syndrome (HPS), using receiver operating characteristic (ROC) analysis, with reference to the study design by Allen [3]; (2) to examine risk factors for HPS using Cox regression analysis; and (3) to examine comprehensively serum cytokine/chemokine profiles, using the Wilcoxson signed rank test, with the goal of elucidating the pathophysiology of HPS post allo-HCT. We thus reported the sensitivity, specificity, positive predictive values, and negative predictive values of each serum ferritin cutoff value, using ROC analyses. We found antigen mismatches in human leukocyte antigen in both graft-versus-host and host-versus-graft directions as risk factors, and also that cytokines, including interferon-γ and interleukin-10, and chemokines, including monocyte chemoattractant protein-1 and interferon-γ-inducible protein-10, may be associated with the pathophysiology of post-allo-HCT HPS. Notably, given the study design, the data on risk factor and cytokine/chemokine in our study [2] are distinct from the data – such as sensitivity or specificity data– on the diagnosis of HPS.

Because exaggerated or biased results from diagnostic studies could lead to misunderstanding by clinicians or incorrect clinical decisions, we totally agree with the comment by Dr. Sabour that researchers should report the diagnostic usefulness of a new tool

from the viewpoints of diagnostic precision (reliability) as well as diagnostic accuracy (validity) [1]. Also, in this context, internationally accepted STARD (Standards for Reporting Diagnostic Accuracy) 2015 guidelines would be a great help [4]. Although the sensitivity and specificity of a test clearly represent its diagnostic accuracy, it is incumbent upon us to report not just specific values of its diagnostic accuracy, but also the confidence intervals, as a measure of its precision [4–6]. In this context, since our study has reported each estimate of serum ferritin diagnostic accuracy with 95% confidence intervals [2], our method of reporting essentially follows STARD guidelines. For clinical use, additional analyses with different populations are needed to confirm the diagnostic precision of serum ferritin for post-allo-HCT HPS, as suggested by Sabour. Also, changes in laboratory personnel, laboratory methods, sample storage, or sample transportation procedures may all influence the reliability of measuring the biomarkers [7]. Thus, as Sabour suggests, kappa or weighted kappa statistics for categorical data and intraclass correlation coefficients for continuous data, should be used to assess agreement and consistency across tests [7–9]. Regarding our study, since using the same automated analyzer with the same chemiluminescence immunoassay kit would contribute to an excellent reproducibility in the measurement of serum ferritin levels, not having assessed the intraclass correlation coefficient of the serum ferritin levels (continuous variable) would have less influence on the interpretation of our ferritin data [7,8]. Therefore, it is different from the study situation in which both within-observer and

between-observer variabilities could have a non-negligible influence on evaluating the diagnostic reliability of a test such as an imaging test.

When comparing the diagnostic value of an index test (i.e., the test being evaluated) with a reference standard, we agree with Sabour that the added (incremental) value of the test should be reported using the ROC curve [10]. In addition, STARD guidelines state that reporting incremental accuracy from combining tests, relative to a single test, can be more informative [4]. We were unable to report such data in our study, because of the lack of a standardized diagnostic biomarker that can be used as a reference standard for HPS.

Other potential limitations in the interpretation of our results include the heterogeneous population and small number of events. However, our main conclusion is based on the results of conventional risk factor analyses using a Cox proportional hazards model, but not on results of diagnostic analyses using a ROC curve. Thus, we believe that the conclusion we have drawn is appropriate, and is not affected by methodological issues.

Potential conflict of interest

None.

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