Dear reviewer

Thank you for your kind review of our manuscript and valuable suggestions.

First, this study did not aim to present a new and better biomarker for GVHD.
Therefore, we could not compare it with existing biomarkers such as inflammatory cytokines of TNF-α, IL-6, IL-18, sIL-18 and so on. We have reported the usefulness and novelty of dielectric relaxation strength as a biomarker from a new perspective when considering the pathology of GVHD.

The changes in the dielectric properties of blood examined this time are not specific to GVHD. It is thought that a change in the dielectric properties of whole blood can occur in any of the condition that causes a change in composition of plasma that promotes the formation of erythrocytes aggregations. The classically well-known acute inflammatory changes are one of them, and as mentioned earlier, the parameter called ESR is thought to indirectly reflect similar phenomena.

We believe that the changes in the dielectric properties of whole blood that we examined here reveal old and new aspects caused by both acute and chronic inflammation.
We are not claiming that changes in the dielectric properties of whole blood are superior to the previously reported various biomarkers of GVHD. The pathway by which severe GVHD leads to irreversible organ failure is not necessarily limited to direct organ damage caused by the GVH reaction by the alloimmune response, but it is thought that secondary and latent circulatory disorders are also greatly involved. From this point of view, we believe that the changes in the dielectric properties of whole blood examined this time provide a new perspective for understanding and management of GVHD.

I added an addition to the Discussion section to clarify this point describe above (line 300-315). In this discussion, we cited a new reference (ref 46).

In addition, we rewrote the summary section into a structured format in accordance with the journal's guidelines (line 25-50).

We hope this revision is satisfactory and will be accepted for publication.

Best regards,

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Dear chief editor

I appreciate your kind review and critical comments.
I will answer and respond to your comments as below.

Comments on Pathophysiology of acute graft-versus-host disease from the perspective of hemodynamics determined by dielectric analysis.

The manuscript is very interesting and novel, but it has the problem that its content is almost unknown for clinicians. The authors try to mitigate this problem explaining what is dielectric analysis, but in Methods section, not in the Introduction, precluding almost all the readers get interest in the further text.
➡
The principle of permittivity measurement was explained in the methods section in an easy manner to understand with schematic illustrations.
However, there are various discussions about how the state of blood cells in a solvent affects the dielectric constant. As we have reported (ref 15), the change in the shape of the red blood cell surface due to further regression from the aggregation state is complex, resulting in changes that are opposite to aggregation. Therefore, it is difficult to provide a clearer explanation than this, and since there are some things that have not been determined, I think it will be inaccurate. Further explanation is beyond the scope of this paper.

Moreover, authors intent to explain what they do showing the data of two representative patients, one with and the other without graft versus host disease, but are those results consistent with the other patients from Table 1?

➡

Figures 3 and 4 show the most typical examples. In other transplant cases, there are events other than GVHD that affect whole blood dielectric constant, such as bacteremia and sepsis, so it is not simple. I think it can be understood a little in Figure 7.

In results section it is stated that "Decreased expression of band 3 is one of the causes of hereditary spherocytosis". Who did mention that a patient has that disease? Does hereditary spherocytosis need a hematopoietic stem cell transplantation (HSCT)? I think not, but it is not easily understandable why do authors mention it. Figure 8 is amazing, but it is not understandable how dielectric analysis is able to explain it.

➡

In this context, the decreased expression of band3 is not related to spherocytosis but is due to degradation by activated Calpain, which we demonstrated in a previous our report (ref 37) and other report (Proc Natl Acad Sci U S A. 1994;91(17):7879-83.), and explained in the discussion (p10, line 21-23, p11, line 16-18). The description has been revised to avoid misunderstandings (p7, line 24-25).

In summary: I did not understand neither the full technique of dielectric analysis, its clinical usefulness nor the possible application in HSCT, but, anyway, I got interest in further learning in that topic. I think that the manuscript is suitable to be publish in the Journal, but I suggest a friendlier description of dielectric analysis and how can collaborate this technique in the clinical care of HSCT patients.

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Changes in the dielectric constant of whole blood are not necessarily specific to GVHD as mentioned in the discussion (p12, line 6-7). We believe that more detailed and quantitative analysis of permittivity is necessary for clinical significance. This paper merely shows that possibility (p12, line 11-16). As mentioned in the introduction, we believe that vascular endothelial disorders and coagulopathy are

very important factors in the pathology of GVHD. My purpose in this article is to present a new way of thinking about the pathology from the perspective of changes in the dielectric constant of whole blood. Please think of Figure 8 as an illustration containing some hypotheses from this perspective as the title of out paper suggests. We added future prospects in the conclusion (p12, line 19-21)

I would be grateful if my answer could help resolve your doubts or questions.

Sincerely yours,

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