

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This review is reasonably synthesized but several aspects require further improvements.

1. It is suggested to add subheadings to the part of “MEASUREMENT OF MITOCHONDRIAL DYSFUNCTION” to make the article more organized.

Response – We agree with this suggestion, and we added subheadings on this section: mitochondrial biogenesis, mitochondrial DNA, qualitative measurements of mitochondrial metabolism, and respirometry.

2. The content of the potential methods for assessing mitochondrial metabolism in the intensive care settings is less. Please continue to consult the relevant to enrich the content.

Response – Thank you for the advice. In this new version of the manuscript, we included a new subsection exploring the aspects related with mitochondrial biogenesis. This subsection deals with data related to the pathophysiological process related to mitochondrial biogenesis, citing the few studies in clinical settings that justify the assessment of biogenesis as an effective measure of mitochondrial activity – page 8. We have also added a new topic in this section, related to practical aspects of assessing mitochondrial metabolism, especially in peripheral cells. We also added a new paragraph in the “respirometry” section, exploring colorimetric assays. It is the last paragraph of this section – page 11. With this, we reiterate the benefits of mitochondrial qualitative assessment, with regard to costs and logistical aspects, by proposing a mitochondrial assessment method for the clinical setting.

3. Authors are encouraged to present figure 1 and figure 2 in colour.

Response – we presented colored versions of figure 1 and figure 2 in this new version of the manuscript. Thank you for the advice.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: In this manuscript, the authors elaborated the pathophysiological mechanisms and main measures of mitochondrial dysfunction in sepsis and explored mitochondria as potential biomarkers for prognosis of sepsis and their relationship with organ failure. The manuscript was well organized and its content was detailed, however, there are some issues should be addressed.

1.Excessive induction of autophagy can lead to apoptosis. Some signaling pathways in autophagy process are related to ROS, and it would be better if the specific pathways could be described in detail.

Response – Thank you for the advice. We agree with this suggestion. In this new version of the manuscript, we included a description of ROS pathways on second and third paragraphs of “physiopathology” section – pages 4 and 5.

2. Many inflammatory mediators contribute to changes in mitochondrial metabolism, and several typical mediators, such as interleukin, can be cited. The content is more convincing.

Response – In fact, there are an important crosstalk between immune response (based on IL expression) and mitochondrial metabolism, especially in monocytes/macrophages and lymphocytes. We describe the most important points of these interaction in the “Mechanisms of mitochondrial dysfunction” section, in a new subsection, entitled “What is the interaction between mitochondrial metabolism and inflammatory activity in sepsis?” – pages 6 and 7.

3. It is still necessary to determine the most practical measurement methods as well as clinical applicability.

Response - We agree with the suggestion and have included a new subsection exploring this issue. It's in the section “Measurement of mitochondrial dysfunction”, subsection “which cells are ideal for measuring mitochondrial activity? And what is the most suitable method?” – pages 11 and 12.

4 LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

As the revision process results in changes to the content of the manuscript, language problems may exist in the revised manuscript. Thus, it is necessary to perform further language polishing that will ensure all grammatical, syntactical, formatting and other related errors be resolved, so that the revised manuscript will meet the publication requirement (Grade A).