Editorial: mitochondrial respiratory chain activity—a potential link with disease severity and treatment response in alcoholic hepatitis. Authors' reply

We thank Dr. Singal for his thoughtful editorial and interest in our article,[1] highlighting the clinical significance and future prospects of our results.[2] As Dr. Singal points out, we assessed the activity of the five mitochondrial respiratory chain (MRC) complexes in patients with alcoholic hepatitis (AH) with various degrees of severity. MRC activity was markedly decreased in AH compared with healthy subjects, and those with severe AH had lower activity than patients with non-severe AH. In fact, we found a strong negative correlation between MRC activity and the disease severity measured by both MELD and Maddrey's index. Also, complex I and III activity positively correlated with corticosteroid response and mortality rates. Noteworthy, we have preliminary unpublished results comparing the MRC activity of these patients with other aetiologies of liver disease. Interestingly, patients with NASH also showed a significant decrease in all MRC complexes, according to previous studies reporting hepatic mitochondrial dysfunction in high fat diet-fed mice[3] and in vitro experiments with HepG2 cells exposed to saturated fatty acids.[4] On the contrary, patients with cirrhosis seemed to have a mild decrease in mitochondrial activity, although these changes were modest compared to those observed in our cohort of patients with alcoholic hepatitis.[1] These findings suggest that MRC dysfunction is more affected in conditions where steatosis is a key feature, but the extent of the mitochondrial dysfunction observed in patients with AH appears to be a specific feature of this life-threatening liver disorder and is linked to severe outcomes such as lack of response to corticoids and mortality.

The main strength of our study relies on the large number of well-characterised patients with biopsy-proven AH to whom hepatic MRC activity was determined. However, we realise our findings are of limited application in clinical practice, at least in the short term, due to that assessing hepatic activity of MRC complexes requires a significant amount of liver tissue and time-consuming laboratory techniques, which are impractical in the majority of clinical settings. For that reason, on the basis of our recently published results, we urge to identify non-invasive blood-based biomarkers with high accuracy to assess hepatic MRC activity in AH patients. As Dr. Singal rightly stated in his editorial, there is a number of emerging and promising non-invasive biomarkers to assess mitochondrial dysfunction in patients with alcohol-induced liver disease determining mitochondrial bioenergetics and metabolomics in peripheral blood monocytes[5,6] as well as measuring circulating liver-specific extracellular vesicles.[7] Unfortunately, the accuracy of these biomarkers in AH patients still remains to be determined and we believe; therefore, there is an urgent need to validate, in large and distinct cohorts of patients with AH, the sensitivity and specificity of non-invasive blood-based biomarkers to measure hepatic MRC activity in order to personalise therapeutic interventions aimed to improve the prognosis of patients with this life-threatening liver disorder.

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AUTHOR CONTRIBUTIONS

Pablo Solís-Muñoz: Writing – original draft (lead). **María de la Flor-Robledo:** Writing – original draft (supporting). **Carlos Ernesto Fernández-García:** Writing – review and editing (equal). **Águeda González-Rodríguez:** Writing – review and editing (equal). **Carmelo Garcia-Monzon:** Writing – review and editing (lead).

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

LINKED CONTENT

This article is linked to Solís-Muñoz et al papers. To view these articles, visit https://doi.org/10.1111/apt.17434 and https://doi.org/10.1111/apt.17440

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