

September 28<sup>th</sup>, 2022

Dear Editor-in-Chief,

attached to this document, you will find a manuscript intended for publication as a **Minireview [Invited Manuscript ID 06196795]** in the **"World Journal of Gastroenterology"** entitled

**"Clinical and pathophysiological understanding of the Hepatorenal Syndrome (HRS): Still wrong or still not exactly right?"**

We kindly ask for permission to use this title instead of the initially proposed title **"Hepatorenal Syndrome - Is that it?"**. In case you allow us to do so, we would like to propose to use the short title as running head in the submitted version.

The manuscript abstract has been accepted by the WJG on 2022-07-05.

**Abstract:**

The Hepatorenal Syndrome (HRS) is one major extrahepatic complication of end-stage liver diseases, hallmarked by renal failure. While circulatory dysregulation is considered a primary etiology for HRS, cirrhosis-related (systemic) inflammation and/or cardiac dysfunction may also play a key pathogenic role towards HRS development. Exclusion of other causes of renal failure Syndrome-Acute Kidney Injury (HRS-AKI) is required for facilitating diagnosis of Hepatorenal by the definition of the International Club of Ascites-Acute Kidney Injury (ICA-AKI). However, understanding of the pathophysiology of HRS is still in progress and there are still limited therapeutic options. Reversibility of renal dysfunction after liver transplantation attests to a functional disorder that signifies altered cellular function. This Minireview challenges simplified views of the HRS in the context of diagnostics and therapy and stresses the need for further evidence as to the transient nature of this syndrome and the interplay between systemic inflammation and the onset of kidney-related hypometabolism.

As the corresponding author, I assure you that the submitted material has not been published or submitted for publication elsewhere. Below, you will find our list of suggested reviewers for this manuscript with knowledge in the field.

We are looking forward to hearing from you on behalf of all authors.

Most sincerely,



Antonios Katsounas, MD  
Professor of Medicine

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#### Suggested Reviewers:


Prof. Frank Tacke, Charité Universitätsmedizin Berlin, Department of Hepatology & Gastroenterology, Campus 18, Virchow-Klinikum and Campus Charité Mitte, Berlin, Germany; [frank.tacke@charite.de](mailto:frank.tacke@charite.de)

Prof. Jonel Trebicka, Department of Internal Medicine B, University of Muenster, Muenster, Germany; [jonel.trebicka@ukmuenster.de](mailto:jonel.trebicka@ukmuenster.de)

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#### Appendix: Positive response to this invitation

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Column Name	Status	Manuscript Title	Manuscript Abstract	Manuscript ID	Accept Date	Remind Date	Decline Date	Close Date	Received Date	Manuscript Status
Minireviews	Kind Remind	Hepatorenal Syndrome - Is that it?	The Hepatorenal Syndrome (HRS) is one major extrahepatic complication of end-stage liver disease, hallmarked by renal failure. While circulatory dysregulation is considered a primary etiology for HRS, cirrhosis-related (systemic) inflammation and/or cardiac dysfunction may also play a key pathogenic role towards HRS development. Exclusion of other causes of renal failure is required by the International Club of Ascites-Acute Kidney Injury (ICA-AKI) to meet diagnosis criteria for Hepatorenal Syndrome-Acute Kidney Injury (HRS-AKI). However, understanding of the pathophysiology of HRS is still in progress and there are indeed limited therapeutic options along with a poor prognosis. Moreover, reversibility of renal dysfunction after liver transplantation suggests a functional disorder. Against this background, this mini-review challenges potentially over-simplified and/or controversial views of HRS and expands upon blind spots and open questions related to diagnostics and therapy.		2022-07-05	2022-08-31				

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