**To:** Editors-in-Chief, World Journal of Hepatology

**Re:** "**Fractional Excretion of Sodium in Hepatorenal Syndrome: Clinical and Pathological Correlation**"

August 22, 2016

**Dear Drs. Balsano and Chuang,**

On behalf of my fellow author, I would like to submit a revised version of the above titled manuscript for publication in WJG. Also included is a detailed point-by-point response to the Reviewers' concerns. The necessary changes have been made to the original manuscript and these changes have been highlighted. We hope that the manuscript now merits publication in your reputable journal.

Sincerely,

Hani M Wadei, MD, FASN, FAST

**Reviewers' response**

**Response to Reviewer #1 (Reviewer number 54593)**

We thank this Reviewer for his positive comments and for bringing important comments that helped us improve the manuscript.

**Point#1**
The Reviewer is bringing up the issue that diuretic use would have affected urinary sodium excretion.

**Response:**
We agree with the reviewer on this point. The majority (72%) of the patients in this study were using diuretics at the time of 24 hr urinary assessment and FeNa calculation. We compared the 24-hr urinary sodium excretion, the random urinary sodium, the FeNA between those on diuretics and those not on any diuretic treatment. Results indicated that diuretic use did not affect any of the urinary sodium indices. We added the results of this analysis to the manuscript in both results and discussion sections. Since we did not adjust for the diuretic dose/type, we made it clear that this a limitation of the study and we added a statement in this regards to the limitation section.

**Changes:**
Results section, 2nd paragraph

To assess the effect of diuretic use on the performance of FeNA <1% in HRS diagnosis, we compared urinary sodium indices between patients on diuretics (n=64) and those not on diuretic (n=24) treatment. There was no observed difference in the 24-hour urinary sodium excretion, FeNa (as a continuous variable) and number of patients with FeNA<1% between those using and not using diuretics at time of FeNa calculation (P>0.3 for all). Also, the sensitivity (100%), specificity (12.5%), PPV (14%) and NPV (100%) of FeNA<1% in diagnosing HRS did not differ when patients not using diuretics were excluded from the analysis.

Discussion section, 2nd paragraph
It is also important to mention that diuretic use did not affect urinary sodium indices or the performance of FeNa <1% in HRS diagnosis which support the avid sodium retention state in these patients with advanced cirrhosis.

Discussion section, 3rd paragraph
The results of the current study indicate that the sensitivity and specificity of FeNa < 1% in the diagnosis of HRS is much different than in non-cirrhotic patients with prerenal

azotemia and that they are not affected by diuretic use. Probably this difference is due to the intense renal vasoconstriction manifesting in cirrhotic patients with subsequent increase in renal sodium reabsorption and the diuretic resistant state these patients develop with worsening liver disease.

Discussion section, paragraph before last
Another important limitation of the study is the lack of detailed information on dietary sodium intake and doses and class of the diuretic medications used.

**Point#2 (Reviewer # 03474959)**
The Reviewer is asking to tone down our conclusions as this is a retrospective study.

**Response:**
We agree with the Reviewer. We toned down the conclusion.
**Changes:**
Abstract
HRS diagnosis should be avoided in patients with FeNa > 1%.
Core Tip
We deleted this statement ""

Discussion section, conclusion paragraph
Our results also indicate HRS diagnosis should be avoided in patients with FeNa higher than 1%.

**Point#3**
The Reviewer is asking for the cause of ESLD and the MELD scores for the study patients.

**Response:**
We thank the Reviewer for bringing up this point. We added the cause of ESLD and the MELD score to Table 1.

**Changes**
**Updated table 1 with these information**

**Point#4**
The Reviewer is asking if patients with fulminant hepatic failure were excluded.

**Response:**
None of the patients who had fulminant hepatic failure were included in this analysis mainly because patients with fulminant hepatic failure and renal dysfunction are considered to have acute kidney injury and do not require kidney biopsy in our institution. We clarified this issue in the Methods section.

**Changes:**
Methods section, 1st paragraph

Patients with fulminant hepatic failure were not included.

**Point #5**
The Reviewer is pointing out that 40% of the patients had diabetes and this could have affected their renal function.

**Response:**
We agree with the reviewer. As pointed out in the manuscript, kidney biopsy was done on this patients as the majority had risk factors for chronic kidney disease (CKD) and therefore we were not sure if their renal dysfunction was related to CKD or hepatorenal physiology which triggered the kidney biopsy. Irrespective of their kidney function or the etiology of their renal disease, FeNa<1 performed poorly in detecting heptorenal syndrome.

**Changes**

None

**Response to Reviewer #2**
We thank this Reviewer's for his constructive remarks.

**Point #1**
The Reviewer is concerned regarding interfering effects of diuretic use on the results presented in Figures 3 and 4.

**Response:**
We agree with the Reviewer. We addressed this point in the response to Reviewer #1, Point#1. As mentioned, we did a sub-analysis and diuretic use did not affect urinary sodium indices probably because these patients had advanced liver disease and were becoming diuretic resistant. We also re-analyzed the correlation between the degree of IF and GS in those using and not using diuretics and the results were identical. We added a statement in this regards in the results section.

**Changes**
**See response to Reviewer #1. In addition we did this change:**

Results section, 3rd paragraph
This lack of correlation was not affected by diuretic use (data not shown)