

February 17, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 8667-Edited.doc).

Title: The role of cystatin C and renal resistive index in assessment of renal function in patients with liver cirrhosis

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The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer (1)

1. Do you have inulin clearance data? You correctly write in your discussion, that inulin clearance is the gold standard to measure renal function, therefore I would suggest to show these data.

Answer: Unfortunately, inulin clearance data were not available during our study and we are aware of this limitation. An explanation was given in Discussion section (page 12, lines 7-9) and now reads: Inulin clearance is impractical because of the necessity for steady-state infusion, a urine bladder catheter, and possible interference from blood glucose (Shemesh et al). Also, it is a costly procedure and we had limited funding.

2. You also correctly state that creatinine is dependent on muscle mass. Do you have data on nutritional status (for example subjective global assessment or handgrip strength) or laboratory parameters (for example pre albumin) to show this.

Answer: The sentence in the Materials and Methods (page 7 lines 11-13) has been added: Referent values for 24-h urinary creatinine excretion were 23 mg/kg ideal body weight for men and of 17 mg/kg ideal body weight for women; Two more sentences in the Results (Page 9, lines 17-19) have been added: Mean values for 24-h urinary creatinine excretion for men was 18.3mg/kg, and for women 16.3 mg/kg.

Decreased creatinine values were detected in 32/47 (68%) men and 9/16 (56.3%) women; Furthermore, a sentences in the Discussion (Page 12, lines 14-17) have also been added: We report that reduced urinary creatinine excretion in cirrhosis correlates with anthropometrically estimated muscle mass and is not related to reduced liver function. Our results are consistent with previous study conducted by Pirlich et al.

3. You state that CysC better reflects renal function, however, I am missing any outcome data such as development of complications (e.g. HRS) or mortality data.

Answer: Indeed this would be useful, but we followed a case-control study design.

4. Your discussion contains a lot of information, however, I am missing a "common thread".

Answer: Discussion has been changed accordingly. We emphasised major findings and shortened the sentences of less importance. Please refer to Discussion section (pages 12-15).

Reviewer (2)

5. There have been some papers that showed the role of cystatin C and renal resistive index for the assessment of renal dysfunctions in patients with liver cirrhosis. The authors should clearly mention the original points of this report.

Answer: El Shazly et al. also compared cystatin C with urea, serum creatinine, RRI and Child-Pugh score, in patients with viral C cirrhosis and reported significant positive correlations (page 14 lines 23-25). We noted that Ustundag et al. conducted a research similar to ours and reported their original points (page 14 lines 25-29): Ustundag et al. noted serum CysC but not serum creatinine or RRI measurement, correlated with GFR, (GFR was estimated by technetium (99m)-diethylene triamine pentaacetic acid renal scintigraphy), in each stage of liver failure.

6. It would be better to show the correlation of renal parameters with MELD score (Table 2) in a plot figure.

Answer: Comment has been accepted. Table 2 was converted to plot figure (page 23).

7. Cystatin, found in the text, should be cystatin.

Answer: Comment has been accepted and changed accordingly.

Reviewer (3)

8. Although the topic is clinically relevant and interesting, the study is not novel. The correlation between Cystatin C- RRI and the severity of cirrhosis and renal function is not unexpected and has been previously shown. The authors should emphasize the novelty of their results.

Answer: The novelty of our results was highlighted. Our data showed that RRI significantly correlated to GFR_{Cys} and that RRI and GFR_{Cys} represent sensitive indicators of renal dysfunction in patients with liver cirrhosis. These methods are non-invasive, non-expensive, and easy to use in routine clinical practice (page 14, page 15). Although similar studies were published, according to our knowledge, no previous studies have correlated these two specific indicators. Discussion has been changed accordingly. This issue has also been addressed on a previous page.

9. Sacerdoti et al. demonstrated an impairment of renal Doppler indices in cirrhotic patients with ascites. The authors should specify the number of patients with ascites and the impact of ascites on their results.

Answer: In our study, 36 patients without ascites (57%) and 27 patients (43%) patients with ascites were included. Following sentence was added (page 10 lines 28-29): RRI was already more increased in 27 (43%) patients with ascites when compared to 36 (57%) without ascites ($p = 0.005$). We have demonstrated these results even more precisely in regards to Child-Pugh classification (Table 1, page 22).

10. In the title and in the section of Introduction the authors should state more clearly the clinical setting in which this investigation was conducted (stable or complicated cirrhotic patients).

Answer: The clinical setting was explained in more details in Materials and Methods section (page 6).

11. In many cases the authors chose references of secondary importance. For example a recent paper (2013) of Mindokoglu et al. published on Hepatology must be mentioned.

Answer: References were corrected accordingly.

12. The authors should describe the medications of the patients and the impact on their results.

Answer: All patients that used medication with possible influence on results were excluded from the

study. This was emphasised in Materials and methods section (page 6 lines 22-25): Patients receiving corticosteroids, antiviral agents, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, aminoglycosides, nonsteroidal antiinflammatory drugs, and L-arginine L-ornithine, were excluded from the study.

13. In this study GFR was estimated as GFR creatinine and GFR cystatin C to evaluate the clinical importance of cystatin C for the determination of renal function. Why did the authors not use a gold standard validated method as ^{51}Cr -EDTA GFR or inulin GFR.

Answer: This issue has been addressed on the first page, first comment. ^{51}Cr -EDTA was not available in our institution.

3 References and typesetting were corrected.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,



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