Reviewer #1:
Scientific Quality: Grade C (Good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Major revision
Specific Comments to Authors: This was an interesting review paper regarding the interplay between gender, liver disease and kidney disease. The paper summarized the most important findings regarding kidney dysfunction in patients with liver disease highlighting the difference between males and females, according to diagnosis and prognosis. In my opinion, the paper is easy to understand and provides current knowledge on this topic, especially for non-expert readers. The paper did not add novelties in the field, however. Major comments - Serum creatinine is less accurate in women for diagnosis of acute kidney injury, especially in the setting of decompensated cirrhosis where patients are sarcopenic. Newly released guidelines consider an increase of baseline serum creatinine > 30% irrespective of a fixed threshold to diagnose HRS-AKI stage 1. Do the Authors believe that this new classification will rebalance this issue between males and females? - Similarly, the lower response to therapy in females can be due to the severity of AKI-HRS (at similar p-creatinine values). - I think that a brief discussion about different methods for GFR evaluation beyond biomarkers may be of help. - I think that AKI (pre, renal and post-renal) on CKD (e.g., diabetes) are commonly seen than in the past in patients with cirrhosis. Have data been published regarding the gender role on this topic? - I agree with the Authors regarding the low response rate in female patients with AKI-HRS, regardless therapies. I agree with them regarding the indication to CRRT. Nevertheless, this indication is linked with LT chance only in cases with AKI-HRS. Patients with NTA (e.g., after iodinate contrast) may have a probability of recovery which is not linked with liver disease. - I do not see table 1. Minor comments - Figure 1. Post-renal causes are not mentioned. Moreover, the Figure is quite confusing since it seems that AKI, AKD and CKD represent different stages of the same disease (according to the time line at the bottom). I suggest to modify this Figure - Figure 2. HRS-AKI is diagnosed in patients with cirrhosis AND ascites. Therefore, this point should be highlighted. - I think that viral hepatitis associated renal dysfunction may be enumerated among CKD and not AKI.

Reviewer #2:
Scientific Quality: Grade D (Fair)
Language Quality: Grade C (A great deal of language polishing)
Conclusion: Major revision
Specific Comments to Authors: The article is within the scope of the magazine, and deals with an interesting topic. It is well written. The reading is fluent. However, it cannot be accepted under the current conditions: 1) The article is not structured. It should be organized in the standard way: introduction, materials, methods, results, discussion, and conclusions. 2) It would be necessary to add a state of the art 3) A discussion section is especially important in which the work presented is compared with other similar ones and the advances and limitations are indicated. 4) The introduction should be improved to explain what are the objectives of the work presented.

2 Editorial Office's comments
1) Science Editor: The manuscript has been peer-reviewed, and it' s ready for the first decision.
2) Company Editor-in-Chief: I recommend the manuscript to be published in the World Journal of Clinical Cases. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

Response to Editors:

R1 Comment 1: *Serum creatinine is less accurate in women for diagnosis of acute kidney injury, especially in the setting of decompensated cirrhosis where patients are sarcopenic. Newly released guidelines consider an increase of baseline serum creatinine > 30% irrespective of a fixed threshold to diagnose HRS-AKI stage 1*. **Do the Authors believe that this new classification will rebalance this issue between males and females?**

We thank the reviewer for this question. We feel we have adequately addressed the poor utility of serum creatinine in women with cirrhosis, however, agree a discussion of how the new definitions will affect this gender bias would strengthen the paper. We have included the following text: "*There are currently no sex specific diagnostic criteria for AKI, AKD, or CKD in CLD. We would like to highlight that it is unclear whether the change in diagnostic criteria will completely address under diagnosis in women relative to men. While studies have shown the required change of 30% serum creatinine occurs at similar rates of men and women with cirrhosis and AKI, this relies on capturing patients at baseline. Given many patients with cirrhosis remain unrecognized until first presentation (14), it is possible that women may already have renal impairment despite a normal presenting serum creatinine. "*

R1 Comment 2: The lower response to therapy in females can be due to the severity of AKI-HRS (at similar p-creatinine values). **I think that a brief discussion about different methods for GFR evaluation beyond biomarkers may be of help.**

We thank the reviewers for this suggestion. We have updated the text to expand our discussion of alternative ways to measure renal function as follows: "This disparity has led to identification of strategies to monitor kidney function in decompensated liver disease. *Measuring GFR directly (using exogenous substances) may better approximate renal function in women (88). However, this is time consuming and difficult to complete during acute decompensation and in the hospital setting. Likewise, using urine output-based definitions of kidney injury in theory would have less sex differences because these are based on volume per kilogram. While less expensive than obtaining a measured GFR, monitoring intake and output in the hospital is labor intensive and requires patients' strict adherence or the insertion of a urethral catheters, which increases risk of infection and is not indicated in most patients outside of the intensive care setting. MicroRNA have garnered attention as innovative markers to evaluate kidney injury in cirrhotic patients due to their ability to differentiate ATN and HRS. However, pre-clinical models have shown these markers are expressed variably across sexes (89).* Fortunately, there is increasing literature on alternative biomarkers for renal function. Two newer markers shown to be predictive of renal dysfunction in cirrhosis include cystatin C (CysC) and neutrophil gelatinase-associated lipocalin (NGAL) (90)."

R1 Comment 3: I think that AKI (pre, renal and post-renal) on CKD (e.g., diabetes) are commonly seen than in the past in patients with cirrhosis. *Have data been published regarding the gender role on this topic?*

This is a great question raised by the reviewer. Unfortunately, there is no clear data published on how gender affects the changing incidence of AKI on CKD in cirrhosis patients to date. It may be possible that this is related to the increasing incidence of CKD in general in patients with cirrhosis as CKD increases risk of AKI. CKD is more common in women with cirrhosis, which we have addressed in the paper. However, unfortunately, there is no clear data published on how gender affects the changing incidence of AKI on CKD in cirrhosis patients to date.

R1 Comment 4: I agree with the Authors regarding the low response rate in female patients with AKI-HRS, regardless therapies. I agree with them regarding the indication to CRRT. Nevertheless, this indication is linked with LT chance only in cases with AKI-HRS. Patients with NTA (e.g., after iodinate contrast) may have a probability of recovery which is not linked with liver disease.

We thank the reviewer for their positive feedback regarding this topic and we agree the discussion of dialysis is complex. To address this comment we have amended our language as follows: “Specifically, dialysis candidacy is closely associated with access to and candidacy for liver transplantation *in patients with irreversible severe AKI associated with hepatic decompensation (42, 43).”*

R2: The article is not structured. It should be organized in the standard way: introduction, materials, methods, results, discussion, and conclusions.

We appreciate this reviewer taking the time to read our article. However, the recommendations are not consistent with the expectations of a narrative review article. Rather they align more with an original/hypothesis driven paper. As this is a narrative review, we were unable to address this reviewers comments at this time.

Minor Comments

- R1: I do not see table 1 → Updated text to “Figure 1”
- Figure 1: Post-renal causes are not mentioned. Moreover, the Figure is quite confusing since it seems that AKI, AKD and CKD represent different stages of the same disease (according to the time line at the bottom). I suggest to modify this Figure → Figure was adjusted to focus on 3 main causes of AKI and the timeline has been removed.
- R1: Figure 2. HRS-AKI is diagnosed in patients with cirrhosis AND ascites. Therefore, this point should be highlighted → While HRS is commonly associated with ascites, the underlying pathophysiology is related to portal hypertension rather than ascites. It is thought that changes in RASS system that lead to HRS begin prior to ascites. The clinical surrogate of this is the presence of HRS in patients with acute liver failure, such as alcohol associated hepatitis. For this

reason, we kindly disagree including highlighting ascites as a part of this cascade for the purposes of this figure. An early reference about the “pre-ascites” HRS physiology is included below. To address this comment, we updated Figure 1 to include ascites in the characteristics of HRS.

- Blendis L, Wong F. The natural history and management of hepatorenal disorders: from pre-ascites to hepatorenal syndrome. Clin Med (Lond). 2003 Mar-Apr;3(2):154-9. doi: 10.7861/clinmedicine.3-2-154. PMID: 12737373; PMCID: PMC4952737.

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gross overestimation of urinary tracer clearance by the plasma tracer clearance, while a third study of eight patients did not [92]. As a result, it is recommended that urinary rather than plasma clearance techniques be used in patients with ascites or severe oedema [93–95]. Despite this, most studies in this field continue to rely on plasma clearance to measure GFR for logistical reasons, which unfortunately compromises the validity of the results. A modification of plasma clearance using markedly delayed sampling (24 h) and altered methods to calculate the area under the curve has been proposed but has yet to be sufficiently validated [96, 97]. A novel GFR estimating equation that has been developed in a cirrhotic population using this methodology contains numerous variables in addition to creatinine, including urea, the international normalized ratio (INR), sodium and the presence of ascites, but the method has yet to be validated [89]. Clinical indications for mGFR measurement in cirrhosis include medication dosing and the assessment of potential combined liver–kidney transplantation. Cystatin C–based equations may be considered as a reasonable alternative.

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https://bmcnephrol.biomedcentral.com/articles/10.1186/s12882-021-02561-1/tables/1

measuring true GFR in frmales with exogenous compounds may be needed but this likely doesn’t solve the clinical issue in the case of acute kidney disease, May need to occur after.