To: Lian-Sheng Ma, President and Company Editor-in-Chief
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Column: Meta-Analysis
Title: Chronic kidney disease severely deteriorates the outcome of GI bleeding: A meta-analysis
Authors: Roland Hágendorn, Nelli Farkas, Áron Vincze, Zoltán Gyöngyi, Dezső Csupor, Judit Bajor, Bálint Erőss, Péter Csécsei, Andrea Vasas, Zsolt Szakács, László Szapáry, Péter Hegyi and Alexandra Mikó
Reviewer code: 00045989, 00039316, and 03476438

Dear Editor-in-Chief,

We would like to thank you for the careful evaluation of our study and also thank you for giving us the opportunity to resubmit our paper. We made the recommended additionally analysis of the data and completed the manuscript text according to the reviewers comment.
Please find our response to the reviewers below. We hope that you will find our extended paper suitable for publication.

On behalf of the authors,

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Answers to Reviewer #1 point:

-This present manuscript deals with a well-speculated clinical question, analyzing the role of chronic kidney disease (CKD) and end-terminal renal disease (ESRD) in gastrointestinal bleeding. The design of the meta-analysis is very well conducted including studies comparing patients presenting with GI bleeding and normal renal function or CKD/ESRD. The search strategy, data extraction, quality assessment, publication bias analysis and statistics seems clear and adequate, with a random effects model approach due to presumed heterogeneity of definitions and techniques.
Answer: Thank you for your positive comments.
ACTION: Not needed.

-The main problem of the paper relies on the novelty of the topic and the heterogeneity of the included studies. The authors are analyzing four outcomes, such as mortality, required units for transfusion, rebleeding rate and length of hospitalization. It's already known that mortality is increased in GI among CKD patients as stated by the authors, the required units for transfusion including 4 studies (1983-1996-2010-2010 !) even if statistically significant, may be not clinically relevant or at least very difficult to interpret due to the included studies

and different clinical criteria for transfusion. Indeed, the authors are analyzing studies in a very wide time interval that may completely influence the results.
Answer: You are right. The increased mortality in CKD/ESRD patients is known and it was showed in the included studies, but it had not been reviewed or analysed in such details before. As the prevalence of hypertension and diabetes mellitus, the most important etiological factors for CKD and ESRD is increasing worldwide, , we predict that GI bleedingwith CKD will be a growing problem. According to Ohmori et al the number of patients on hemodyalisis in Japan accounts for the 1/7 of all dialysis patients worldwide (PMID: 22728474).
Thank you for highlighting that in different centers the clinical criteria for transfusion may differ, however transfusion remaines a key indicator in the treatment of GI bleeding, therefore we performed a meta-regression which did not show difference in required units for transfusion since the 1980's (b = –0.0028; 95%CI: –0.0242 –0.0186; P = 0.7972).
You are right, that the wide time interval of the studies analysed may influence the results, therefore we included it in the limitations section. Nevertheless we wanted to perform the most detalied analysis of this clinical problem with the lowest possible bias, thus we included all of the articles written in this topic.
ACTION: The reference of Ohmori et al. was inserted into the discussion session. The result of the meta-regression analysis was added to the results.

Probably, a meta-analysis is not actually the best way to determine the association between GI bleeding and CKD/ESRD. Thus, the justification of the meta-analysis seems poor.
Answer: Your criticism concerning the justification of this meta-analysis is valid. However this meta-analysis allowed us to see that there is an association between poorer outcomes of GI bleeding and CKD/ESRD in cohorts far and apart both in time and geographically.
In this meta-analysis we wanted to highlight the importance of this clinical problem and we share your view and believe that it needs further scientific research. In order to understand the effect of CKD/ESRD and other comorbidities on the outcomes of GI bleeding in more details, observational trials, and registries on GI bleeding should be developed.
ACTION: The discussion was completed.

-Minor concerns: - The authors reported the outcomes related to upper/lower GI-bleeding. What's about small bowel bleeding /OGIB?. There is no comment in this sense.
Answer: You are right, it was logically missing.
ACTION: Both the small bowel bleeding and the OGIB have higher prevalence in CKD. It was added to the second paragraph of introduction with references (PMID: 25608445, PMID: 22728474, PMID: 16937529).

- ESRD should be defined in the main text.
Answer: You are right, it was missing from the introduction.
ACTION: It was added to the text.

- There is so much information regarding the quality of studies and risk of bias. I agree that the methods section is a key point in a systematic review but it seems too long with many

sentences probably unnecessary "According to the Cochrane Handbook[16] "tests for funnel plot asymmetry should be used only when there are at least 10 studies included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry" (with the reference to the Cochrane Handbook should be ok).
Answer: You are absolutely right.
ACTION: It was corrected.

–The authors should discuss more how the comorbidities of these patients presenting with CKD may play a role in the outcomes/GI bleeding influencing the results.
Answer: Thank you for your highlighting this issue. We scrutinized the articles and for further details on comorbidities of the patients with CKD/ESRD.
ACTION: We amended the third paragraph of discussion with these informations.

Answers to Reviewer #2 point:
-The authors undertake a meta-analysis of 6 articles reporting 406,035 patients, 51,315 of whom had impaired renal function. The meta-analysis reinforces multiple previous series that have documented a higher mortality in patients with CKD and ESRD as well as a higher rebleeding rate in those with CKD. ESRD, in turn, was noted to increase transfusion requirements, rebleed rate, and length of hospitalization time compared to controls. There are several limitations of this meta-analysis, some mentioned in the Discussion section. These include: 1. Study heterogeneity in which 383,340 of the 406,035 patients come from a single study and all but 1153 control patients come from this study. Likewise a single study reported outcomes in ESRD patients in 14,483 patients, whereas the other 5 studies reported only 218 additional patients or failed to distinguish CKD from ESRD. The Forest plot square size fails to define the magnitude of these statistics. This requires elaboration in the Discussion section.
Answer: Thank you for your opinion. The Forest plot is only a graphical visualization which is not able to show the clear differences between the sample sizes. To detect if this article with its high number of patients has a high influence on the OR of mortality, we performed a sensitivity analysis. It showed, that removing this article or the subgroup from the analysis would not result in a significant change of the original pooled OR.
ACTION: Sensitivity analysis was performed, we integrated it in the methods, results and discussion.

2. The study suffers from failure to distinguish upper from lower GI bleeding or to define the cause of bleeding in most of the papers reviewed.
Answer: You are right, we agree that this article needs further clarification where the GI bleedings originated from. Based on the search and inclusion criteria we could identify articles with upper GI bleeding only.
ACTION: These informations were added to the first paragraph of the discussion.

3. Although the authors note platelet dysfunction in CKD, the meta-analysis suffers from failure to distinguish between mild, moderate, and severe CKD. Is a patient with a GFR of 50g at the same risk of mortality and rebleeding as one with a GFR of 20? At what GFR does platelet dysfunction become clinically significant?
Answer: We agree, that making subgroup analysis based on severity of CKD could provide more information but unfortunately the included articles do not differ these

groups. In the EPIRAN study eGFR was not associated with risk of death (PMC5111196) but other studies showed independent association between lower eGFR and mortality (PMID:15385656; PMID: 26045089, PMID: 27339450).

A study reported that even mild levels of renal impairment were associated with increased risk for postoperative bleeding after coronary bypass: „patients with a GFR of 40 mL/min or less had six times the odds of postoperative bleeding than patients with a GFR greater than 100 mL/min (odds ratio [OR], 6.51; 95% confidence interval [CI], 1.87 to 22.66); those with a GFR of 41 to 60 mL/min had nearly four times the risk (OR, 3.87; 95% CI, 1.21 to 12.35). Even patients with mild CKD at a GFR of 61 to 80 mL/min were at an elevated risk (OR, 2.11)". (PMID: 12500224)

It is hard to answer at what GFR platelet dysfunction will be clinically significant. A study with 42 CKD patients with (GFR < 30 ml/min) examined skin bleeding time, there was only a weak correlation between calculated GFR and skin bleeding time ($r(2) = 0.1564$) (PMID: 18534067). A study reported that platelet aggregometry does not appear to be useful in measuring platelet dysfunction in heart failure patients with mild to moderate renal impairment, but no severe CKD patients were included (PMID: 27797407). Whole-blood platelet aggregation by the screen filtration pressure method seems to be a promising way of monitoring platelet function for hemodialysis patients (PMID:21426514). Further investigations are neded to answer this question too.

ACTION: Based on the request of Reviewer 3, we omitted this part dealing with platelet disfunction from the third paragraph of discussion.

Answers to Reviewer #3 point:
In the manuscript entitled " Chronic kidney disease severely deteriorates the outcome of GI bleeding: A meta-analysis" authors showed the higher mortality and re bleeding rates as well as higher transfusion requirements and longer in hospital stay of CKD/ESRD patients by meta-analyzing relatively old data. The strength of the manuscript is its rigorous methodology, while old time data and few included studies comprise the limitations.
Answer: Thank you for your positive comment. We agree that an important limitation of this meta-analysis is the inclusion of old data, but we wanted decrease the publication bias as much as possible, therefore we did not exclude data based on the publication year.
ACTION: Not needed.

Major comments 1. Further highlight the significance of meta-analyzing old data in the era of different treatment of GI bleeds. Please evaluate the possibility to conduct subgroup analysis to evaluate the effect of the date of data acquisition on all study outcomes. Metaregression analysis can be an alternative.
Answer: Thanks for the suggestion. We have discussed it with the statisticians, but because of the scarce data we could not perform relevant subgroup analysis for rebleeding, LOH and transfusion requirement outcomes. Several data comes from the same article, (we have only 3 articles and 4 data) so subgroup analysis would not have given further reliable information. However we performed meta-regression for

rebleeding rate and transfusion. The number of required units for transfusion has not changed since the 1980s (b = –0.0028; 95%CI: –0.0242 –0.0186; *P* = 0.7972; r-analog: 0.00, Supplementary Figure 2B). Based on data from 4 articles, no difference in rebleeding rate could be observed in the last 30 years (b = 0.0027; 95%CI: –0.0353 – 0.03; *P* = 0.8726; r-analog: 0.00, Supplementary Figure 2C).
ACTION: Meta-regression in rebleeding and transfusion requirements was performed and its results were inserted into the results session.

2. In the presence of significant heterogeneity regarding mortality, please perform sensitivity analysis to identify study(ies) responsible for the heterogeneity and examine if the exclusion of these studies affects your result. Metaregression analysis can be an alternative too.
Answer: Excellent point! Thank you. We performed sensitivity analysis and meta-regression to identify articles which could explain the high heterogeneity data regarding mortality. Sensitivity analysis showed that removing the studies separately does not influence significantly the main pooled OR of the analysis. Meta-regression showed slight significance (regression coefficient: b = –0.0548; 95%CI: –0.0968 – (–0.0128); P = 0.0105; r-analog: 0.2), in the newest articles the OR is decreasing with the time, so the mortality-rate is lower nowadays than in the 80s and 90s. It likely contributes to the high degree of heterogeneity.
ACTION: Sensitivity analysis and meta-regression was performed and attached as Supplementary Figure 1. Methods, results and discussion sessions were completed with these points.

Minor comments 1. Abstract. Delete the detailed description of the PICO
Answer: You are absolutely right.
ACTION: We have omitted it from the paper.

2. Introduction. Delete the first 10 sentences of paragraph 2, as the provide redundant info
Answer: You are right that these sentences are not closely connected to the main topic of the article, but we wanted to highlight that GI bleeding is a life threating disease and some of the scoring systems for GI bleeding include the renal functions, showing that impaired renal function is an important factor in GI bleeding. We discussed it and we made the decision that we would leave it in the main text.
ACTION: Not needed.

3. Methods Quality of studies and risk of bias. No need to explain why you did not perform Egger's test and at the end of the same paragraph please delete "Articles earned a potential of 2 points for comparability" since the info is confusing and "We compared the groups based on age and treatment with ulcerogenic drugs (nonsteroidal anti-inflammatory drugs and aspirin)" since you did not make these comparisons in your results.
Answer: You are absolutely right.
ACTION: We removed this section from the methods part of the paper.

4. Results Mortality. Please clarify if the mortality OR was higher in the CKD/ESRD group compared to controls or that the OR was different among CKD and ESRD subgroups (not evident, since the CIs overlap)

Answer: You are right. We wanted to give the OR for CKD and ESRD compared to the controls and not between the CKD and ESRD groups.
ACTION: The text was completed in the results and discussion.

5. Discussion, There is also redundant info in this section: you may delete almost the whole 3rd paragraph.
Answer: You are absolutely right.
ACTION: We omitted this part from the discussion.

Please consider to change the statement in this paragraph that "patients ... require almost 2 times more red blood cell units for transfusion" with "patients ... require almost 2 more red blood cell units for transfusion
Answer: We agree.
ACTION: It has been done.