October 17, 2018

RE : World Journal of Gastroenterology-Manuscript no. 41642

Dear Editor-in-Chief,

We are submitting our revised manuscript entitled " **Increased End-stage Renal Disease Risk in Patients with Inflammatory Bowel Disease: a Nationwide Population-based Study** " for publication consideration in *World Journal of Gastroenterology.*

We appreciate the valuable and insightful comments from the reviewers. We responded to each of the comments made and incorporated all modifications suggested by the reviewers into the revised manuscript. Please let us know if you have any further suggestion for changes.

Sincerely,

Joo Sung Kim, MD, PhD.

Authors' Response to the Reviewers' Comments

We thank the reviewers for their thoughtful and expert review of our manuscript and for their valuable and insightful comments. We responded to each of the comments made and incorporated all modifications suggested by the reviewers into the revised manuscript. Changes to the revised manuscript have been highlighted (underlined and in blue). Our responses to the Reviewers' comments are as follows:

Reviewer 1:

1. This is an interesting study and I think overall, this is a well conducted study with good study design. However, I have several important comments.

1) Table 2 RE: Model 2: adjusted for model 1 + place of residence, income, diabetes mellitus, hypertension, dyslipidemia, congestive heart failure, ischemic heart disease, and gout and/or hyperuricemia What happens if you add type of treatment into the multivariate models since treatment type may play an important role.

Reply:

Thank you for your critical comments. We totally agree with your opinion. Please refer to the revised Tables 2 and 3 showing the updated values for based on the results of multivariate analysis with new Cox-proportional hazards model 3. The following sentence is now included in Abstract of the revised manuscript: (page 5, lines 18-24): "Patients with IBD had a significantly higher risk of ESRD than controls (adjusted hazard ratio [HR], 3.03; 95% confidence interval [CI], 1.77–5.20; *P* =<0.001). The incidences (per 1000 person-years) of ESRD were 0.51 in patients with CD and 0.13 in controls, respectively (adjusted HR, 6.33; 95% CI, 2.75-14.56; *P* < 0.001). In contrast, the incidence of ESRD was similar between the UC and control groups (0.37 vs. 0.37 per 1000 person-years; adjusted HR, 2.01; 95% CI, 0.90-4.51; *P* = 0.089)."

Please refer to Results (pages 12-13, lines 26-7): " The ESRD incidence was significantly higher in the IBD cohort compared to controls, after multivariate adjustments for age, sex, place of residence, income, comorbidities and medication use (adjusted HR, 3.03; 95% CI, 1.77-5.20; *P* < 0.001; Table 2). The ESRD incidence (per 1000 person-years) was 0.51 in patients with CD and 0.13 in controls (adjusted HR, 6.33; 95% CI, 2.75-14.56; *P* < 0.001). Among patients with CD in both the incident and prevalent CD groups, the ESRD incidence was also significantly higher compared to controls (Incident CD group: adjusted HR, 6.30; 95% CI, 2.60-15.26; *P* < 0.001; Prevalent CD group: adjusted HR, 6.38; 95% CI, 2.47-16.47; *P* < 0.001). In contrast, the ESRD incidence was not

significantly different between the UC and control groups (adjusted HR, 2.01; 95% CI, 0.90-4.51; *P* = 0.089; Table 3; Figure 1B and 1C)."

2. 2) Is it possible to show mortality data? Is it possible that patients with UC died before turned ESRD? or poor candidate for dialysis?

Reply:

Thank you for your comment. Please refer to Supplementary Tables 2-3. The following sentence is now included in Results of the revised manuscript (page 14, lines 4-15): "***Inflammatory bowel disease as a risk factor for overall mortality***

The overall mortality rate was higher in IBD cohort compared to controls, but there was no statistically significant difference (4.76 vs. 4.48 per 1000 person-years; crude HR, 1.06; 95% CI, 0.98-1.15; P = 0.120; Supplementary Table 2). However, after multivariate adjustments for age, sex, place of residence, income, comorbidities and medication use, IBD cohort showed increased risk of all-cause death compared to controls (adjusted HR, 2.15; 95% CI, 1.84-2.51; P < 0.001; Supplementary Table2). The overall mortality rate (per 1000 person-years) was 4.31 in patients with CD, 2.10 in controls (adjusted HR, 2.79; 95% CI, 2.14-3.64; P < 0.001; Supplementary Table 3), 4.98 in patients with UC and 5.63 in controls (adjusted HR, 1.98; 95% CI, 1.62-2.41; P < 0.001; Supplementary Table 3), respectively."

Please refer to Discussions (pages 18, lines 13-23): "In previous studies, it is still controversial whether IBD increases mortality[53-55]. However, after adjusting for age, sex, complications and medication use, we demonstrated that overall mortality was 2.79-fold higher in the CD cohort and 1.98-fold higher in the UC cohort compared to the control groups. This suggests that IBD itself may be an independent risk factor for death. In our study, the overall mortality incidence in patients with UC was significantly lower than the control group, suggesting that the low incidence of ESRD in patients with UC was not due to premature death of patients with UC before

turning to ESRD or poor candidates of dialysis. However, data on the cause of death could not be obtained from our study, so further study should be conducted on the cause-specific mortality of IBD."

3. 3) In discussion: - Please discuss that Crohn's disease is a cause of Enteric hyperoxaluria, recurrent urolithiasis, and systemic oxalosis PMID: 22366809 - Inflammatory bowel esp crohn's may lead to significant dehydration and electrolyte abnormalities and repeated AKI. PMID: 25599054 - Urinary anomalies, hematuria and proteinuria were found more in patients with crohn's disease than ulcerative colitis. PMID: 22303602 - Inflammatory bowel disease is an important cause of AA amyloidosis: Inflammatory bowel disease and systemic AA amyloidosis. PMID: 23371008, PMID: 12369137, PMID: 12069702 and PMID: 19689697 - IgA nephropathy is the most frequent kidney biopsy diagnosis in IBD and has a significantly higher diagnostic prevalence compared with all non-IBD kidney biopsy specimens. PMID: 24262508 Of note from this CJASN study, IgA nephropathy was the most common diagnosis (24% [20 of 83]), followed by interstitial nephritis (19% [16 of 83]); please discuss - rapidly progressive IgA nephropathy has been described in a patient with exacerbation of Crohn's disease PMID: 22866754 - There is now more reported association between inflammatory bowel disease (IBD) and an increased risk for the development of nonalcoholic fatty liver disease (NAFLD) PMID: 29697458 ; and NAFLD is associated with proteinuria and poor renal outcomes PMID: 29787418 and PMID: 29215435

Reply:

Thank you for your thoughtful comments. As pointed out, the following sentences are now included in Discussion of the revised manuscript (pages 16-17, lines 9-29): Especially in CD, nutritional problems, such as dehydration and electrolyte depletion, are more prominent due to persistent inflammation of the intestine and repeated

intestinal resection, leading to electrolyte abnormalities and recurrent acute renal failure, resulting in CKD[30].

Of the renal manifestations of IBD, the following manifestations are more common in patients with CD. Among the renal manifestations of the IBD, nephrolithiasis may occur in association with fat malabsorption and excessive absorption of oxalate in the intestine of the CD. The prevalence of recurrent nephrolithiasis in patients with CD is up to five times higher than the general population, which may be the cause of the ESRD[31, 32]. Secondary AA amyloidosis, one of the rare complications of IBD, can occur in about 0.3% to 10.9% of patients with CD, from 0% to 0.7% of patients with UC, and can cause proteinuria, nephrotic syndrome and eventually ESRD[33-37]. Asymptomatic urinary abnormalities referring to proteinuria and hematuria were more common in patients with CD than in patients with UC, and these symptoms may be manifestations of glomerular disease, such as glomerulonephritis, which can cause ESRD[38]. Several epidemiologic studies have shown that patients with IBD have an increased risk of developing nonalcoholic fatty liver disease (NAFLD), and up to 33.6% of patients with IBD have NAFLD[39, 40]. NAFLD is also associated with proteinuria and may present poor renal outcome[41, 42]. Therefore, NAFLD may be regarded as a differential diagnosis of asymptomatic urinary abnormalities in IBD and careful consideration should be given to the occurrence of renal insufficiency.

Recently, growing evidence has suggested that IgA nephropathy is closely related to CD[43]. Ambrez et al. showed that IgA nephropathy (24% [20 of 83]), followed by interstitial nephritis (19% [16 of 83]) was the most common diagnosis in patients with IBD who underwent renal biopsy. The prevalence of IgA nephropathy was also significantly higher in patients with IBD than in the general population[44]. In addition, rapidly progressive IgA nephropathy has been reported in a patient with exacerbation of CD[45], suggesting a common pathophysiological relationship between IgA nephropathy and CD. The association between IgA nephropathy and CD might be explained by a direct link between the kidneys and the intestine, referred to as the kidney-gut axis. Intestinal tissues from patients with IgA nephropathy and patients with CD showed increased permeability[46, 47]. The destruction of the intestinal

epithelial barrier causes an increase in pro-inflammatory cytokines and toxins associated with the intestinal microbiota. These conditions facilitate the translocation of endotoxin and microorganisms from the intestine into the bloodstream, which can lead to a systemic inflammatory reaction and uremic toxicity[48]. IgA nephropathy is caused by the accumulation of immune complexes that react to food and microbial antigens. In patients with CD, serum IgG and IgA levels were elevated by a mucosal inflammatory response to *Klebsiella pneumoniae* antigen[49, 50]. In addition, a genetic predisposition to CD may be related to genes involved in IgA nephropathy, such as human leukocyte antigen-DR1[51, 52]. Indeed, IgA nephropathy is one of the most common causes of glomerulonephritis, which leads to ESRD in some patients. Consequently, the fact that the pathogeneses of CD and IgA nephropathy are closely related might explain why patients with CD have a high risk of ESRD. However, in the present study, we did not evaluate the proportion of patients with CD that developed ESRD through IgA-related nephropathy.

4. Minor grammar comments as below: RE "interlukin-6" should be "Interleukin 6" RE previous study have; "study" should be "studies RE previous report have demonstrated; "report" should be "reports" RE "The 5-ASA therapy might not have a protective effect on the development of ESRD, but serve as a confounder that represent relatively mild-to-moderate activity of CD." "represent" should be "represents" RE "rare intractable disease" should be "rare, intractable disease"

Reply:

Thank you for your kind comment. We have corrected all the grammar issues you mentioned.

Reviewer 2:

1. the authors reported an interesting nation-wide study on the association between the IBD and end-stage renal disease. The results are impressing and the study is well written.

I have only a minor comment: was the grade of ESRD evaluable at the time of the study? In other words, all patients were on renal replacement therapy at the time of the study or they have a various degree of ESRD? This could be useful to assess the risk of developing ESRD and, finally, the need for kidney transplantation.

Reply: We are very thankful for your kind comments on our paper. Please refer to Results (pages 12, lines 20-22): "Among the patients of ESRD, 238 patients underwent dialysis and 7 patients underwent kidney transplantation." Unfortunately, the information on the severity of ESRD was not available from the National Health Insurance database, as described in Discussion of the manuscript related to a limitation of this study. The following sentences are now included in Discussion of the revised manuscript (pages 18, lines 25-28): First, because the severity of IBD and ESRD was not available from the NHI database, we could not determine the associations between severity of IBD, risk of developing ESRD, and the severity of ESRD in this study population.