

We are submitting an improved and revised version of our manuscript to be considered for publication in *World Journal of Gastroenterology*

Title: Diagnostic delay in inflammatory bowel disease increases the risk of intestinal surgery

On behalf of all of the authors, I would like to thank the Editor and the Reviewers of *World Journal of Gastroenterology* for taking the time and effort to review our manuscript. We appreciate the thoughtful and constructive comments. After considering these comments, we have performed additional analysis and revised our manuscript to include the requested important clarification. We are resubmitting it for your consideration.

We have provided detailed responses to the reviewers' comments and have prepared a revised version of the manuscript that includes additional details and addresses all of the comments and concerns of the Reviewers.

We hope that this revised version presents more clearly the novel contributions of the study and the validity of the reported data. We hope that, upon review of the revised manuscript, you will find our study worth publishing in *World Journal of Gastroenterology*

Thank you for your consideration.

Sincerely,

Ja Seol Koo, MD/PhD

Reviewer and Editor Comments to Author:

<Reviewer 1 - Comments to authors>

Dong-won Lee et al. is a retrospective analysis of existing medical records (chart review) aiming at investigating the factors affecting diagnostic delay and its effects of diagnostic delay in inflammatory bowel disease. Patient consent was not required/ waived because of the nature of the study but the study was approved by the Institutional Review Board. Not surprising, the results were convincing. According to the authors' observations they found out that a diagnostic delay was associated with poor outcomes in inflammatory bowel disease. The median diagnostic time interval was 6.2 and 2.4 months in Crohn's disease and ulcerative colitis, respectively. Among the initial symptoms, perianal discomfort before diagnosis delay was associated with diagnostic delays in Crohn's disease. No clinical factor was associated with diagnostic delays in ulcerative colitis. Strictureing, and penetrating types were associated with increased intestinal surgery risks in Crohn's disease. In ulcerative colitis, a diagnostic delay was the only factor associated increased intestinal surgery risks. The data of chart review, statistics, results, discussion and citations is convincing. The language is relatively well written except on page 1 there is a misspelling "Korea Universtiy Ansan Hospital", should read - Korea University Ansan Hospital. The paper is publishable

→ We thank the reviewer for this comment. As you have suggested, we have substituted "Korea Universtiy Ansan Hospital" with "Korea University Ansan Hospital".

<Reviewer 2 - Comments to authors>

The authors have addressed an important aspect - diagnostic delay in IBD and the consequences. (1) The authors have studied the diagnostic delay over 15 years- did they see any reduction in diagnostic delay over 15 years?

→ We thank the reviewer for this comment. Because the number of patients enrolled in the study is not large, there is a limit to see the trends over time in each year. We have examined the rate of a long diagnostic delay and diagnostic time interval by the 5-year unit. As shown in below table, the rate of diagnostic delay and diagnostic interval did not changed with time in patients with IBD.

Years	2000-2005	2006-2010	2011-2015	P-value
CD patients				
The rate of diagnostic delay	5/24 (20.8%)	13/48 (27.1%)	23/93 (24.7%)	0.845
Diagnostic interval, days	66.0 (31.5-573.3)	192.5 (46.8-742.5)	220.0 (60.5-642.5)	0.414
UC patients				
The rate of diagnostic delay	3/6 (50.0%)	15/55 (27.3%)	14/69 (20.3%)	0.224
Diagnostic interval, days	232.5 (55.3-1126)	74.0 (32.0-197.0)	72.0 (35.0-162.5)	0.943

(2) Some improvement is needed in statistics in the results- addition of interquartile range to median values.

→ We thank the reviewer for this comment. As you have suggested, we have added the interquartile range to median value in table 1, table 2, supplementary table 1, and supplementary table 4.

(3) The perianal pain was the only clinical factor associated with diagnostic delay as

per this study. How do the authors explain this? would they recommend any suggestion to improve this?

→ We thank the reviewer for this comment. In Korea, CD patients with perianal discomfort tend to visit the colorectal/anus surgery clinic or general doctor's clinic for the first time. However, lack of awareness of IBD in surgeons and general doctor is presumed to be the main cause of delayed diagnosis. Therefore, strengthening IBD education for general and general surgeons is considered to be a good way to reduce the delay of diagnosis of IBD disease, especially Crohn's disease with perianal disease.

We added some explanation regarding issue related to delayed diagnosis in CD patients with perianal discomfort in discussion section, as following:

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"This is related to the tendency of CD patients with perianal discomfort to visit the colorectal/anus surgery clinic or general doctor's clinic for the first time in Korea. However, they might tend to overlook and miss the diagnosis of CD because anal disorders, such as hemorrhoids, are relatively common and IBD is rare in the East than in the West^[19]. Therefore, strengthening IBD education for general doctors and general surgeons is considered to be a good way to reduce the delay of diagnosis of IBD disease, especially CD patients with perianal disease."

(4) Finally they need to explain the finding of diagnostic delay in UC causing increased likelihood- Is it a statistical finding or they feels it is a clinically relevant finding?

→ We thank the reviewer for this comment. This study demonstrated the association between a long diagnostic delays and poor clinical outcomes in patients with UC for the first time. As mentioned in the discussion section, we believe that this result is in part owing to relatively long diagnostic delay compared to those of

other UC diagnostic delay studies and to ethnic differences. In addition, as shown in table 2, the duration from symptom onset to first hospital visit is significantly longer in a long diagnostic delayed group compared with non-delayed group. This difference is caused by various factors such as patient's perception, attitude toward the disease and sensitivity to symptoms, and these factors are thought to influence patient's prognosis. However, as the reviewer pointed out, it is difficult to completely rule out that our result is accidental statistical finding. Therefore, we believe that a large multicenter prospective study is needed to reveal the exact association between the diagnostic delay and prognosis in patients with UC.

We have modified and supplemented the Discussion section as follows:

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“In present study, the duration from symptom onset to first hospital visit is significantly different between the delayed and non-delayed groups. This difference is caused by various factors such as patient's perception, attitude toward the disease and sensitivity to symptoms, and these factors are thought to influence patient's prognosis. However, a large multicenter study is needed to reveal the exact association between the diagnostic delay and prognosis in patients with UC.”

(5) The number of Table need to be reduced

→ We thank the reviewer for this comment. As you have suggested, we reduced one table by switching table 5, which shows the medication history during the following period, into a supplementary table.