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**Column:** Prospective Study

**Title:** Efficacy of noninvasive evaluations in monitoring inflammatory bowel disease activity: a prospective study in China

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Dear Editor Gong:

It is our great honor to hear from you. We thank the reviewers and editors for their constructive comments. These comments allowed us to in depth identify the inadequacies of our paper to improve the quality of it. Please convey our sincere thanks to the reviewers and editors.

Based on the reviewer's comments, we have made major modifications on the original manuscript. For your convenience, we are submitting a marked copy of revised manuscript in addition to a clean copy and response to reviewer's letter. We hope that our revised version will be satisfactory for publication in World Journal of Gastroenterology. Thanks again to you and the reviewers for the time and effort you put towards our paper.

If you have any questions regarding this manuscript, please feel free to contact us. We look forward to hearing from you soon.

Best regards,

Biao Nie

2017-09-15

Response to Reviewer's Letter

Review1:

We really appreciated your conscientious and valuable comments. We followed your comments and added the necessary edits. The main revisions in the manuscript are listed below:

**Comment 1:** The abstract is not well structured, and in particular, the methods and the results sections are too short.

**Response:** Special thanks to you for your constructive comments. Firstly, we acknowledged that the abstract wasn't well structured before. To make our abstract informative and structured, we modified the format of abstract according to the guideline of the World Journal of Gastroenterology and presented the method and results section in detail. We added the FC measurement and data analysis method in method section. In result section, we added the FC level and P values in CD, UC and IBS patients, we also add the Spearman's rank correlation coefficient of noninvasive makers with their endoscopic scores. For modified details please see ABSTRACT section (Page 4 and Page5).

**Comment 2:** The Authors aimed to study non-invasive biomarkers, but then they included the CDAI (which is a disease activity scoring system and not a biomarker).

**Response:** We appreciated your rigorous scholarship and this comment was valuable as it made the manuscript more precise. We substituted evaluations for biomarkers in title and main text.

**Comment 3:** The inclusion and exclusion criteria are not clear.

**Response:** Thank you for your conscientious comments. To make the inclusion and exclusion criteria more explicit, we specified the diagnosis criteria of IBD in inclusion criteria. Also, in exclusion criteria, we modified the age range, elaborated the deceptive reasons for elevated CRP/EST/PCT and confined the time of NSAIDs usage before endoscopic. For details please see inclusion and exclusion section (Page9 and Page10).

**Comment 4:** The sample size is too small to allow sufficient statistical power.

**Response:** Special thanks to you for your kind comments. We acknowledged that our study was a single-center study with small sample size. Firstly, to more accurately reflect the efficacy of FC, we categorized IBD patients into three subgroups, resulting in a relatively small number of patients in each

subgroup. Secondly, although the incidence rate of IBD was increasing in China, the overall prevalence rate was still low when compared with western country. IBD still wasn't a common disease of gastroenterology system in China. Last but not least, as IBD had a chronic relapsing-remitting course, terrified by painful endoscopy experiences and they were reluctant to visit clinicians until the disease manifests by rectal bleeding or obstruction. Those reasons resulting in limited patients involved in the study. However, we will continue devote to the study to enlarge the sample size and follow up those patients, comparing the change from baseline level to reflect the response to treatment, using FC to guide clinicians timely change their clinical regime.

**Comment 5:** The discussion section should start by stating the main results of the study. The Authors should add a full paragraph explaining their results and their clinical significance.

**Response:** This comment is valuable as it make the article more explicit and practical. Following your comments, we started the discussion by stating the main results of the study to make the manuscript concise (Page 20). We also explained the result and added clinical significance in discussion section. For details, please see discussion section (Page23 and Page24).

**Reviewer 2:**

Thank you very much for your recognition and conscientious comments. We faithfully followed your comments and the main revisions are listed below:

**Comment:** Please peruse all numbers (including statistics) again. Moreover, include as exclusion criterion also patients >85 years, am I correct?

**Response:** Indeed, we peruse all numbers again according to your suggestion. Moreover, we were very sorry for puzzling you in the exclusion criteria for age range and we added "age < 18 years or >85 years" in exclusion criteria to make it clear (Page 10).

**Reviewer 3:**

Thank you for your conscientious and valuable comments. The main revisions in the manuscript are listed below:

**Comment 1:** Abbreviations should be defined at the first mention in the text and not only in the abstract

**Response:** Thank you very much for kind reminder. The standard abbreviations were defined in the abstract and in the main body of the manuscript upon first mention in the text according you reminder.

**Comment 2:** The normality of data distribution was visually established with the Q-Q plot. Data distribution should be established with the Kolmogorov-Smirnov or Shapiro-Wilk test as appropriate (see SPSS explore section).

**Response:** Special thanks to you for your good comments. For the data analysis, we only used Q-Q plot to visually show the normality of data distribution. The normality test of the noninvasive evaluations was conducted by using the Kolmogorow-Smimov test or Shapiro-Wilk test as sample size less than fifty. We modified the statement in Statistical analyses section. For the analysis outcome please see below figures.

**Tests of Normality**

	Kolmogorov-Smirnov <sup>a</sup>			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Calprotectin(ug/g)	.293	25	.000	.707	25	.000
CDAI	.135	25	.200	.881	25	.007
血沉	.206	25	.008	.786	25	.000
C反应蛋白	.325	25	.000	.484	25	.000
降钙素	.242	25	.001	.666	25	.000

a. Lilliefors Significance Correction

\*. This is a lower bound of the true significance.

**Tests of Normality**

	Kolmogorov-Smirnov <sup>a</sup>			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Calprotectin(ug/g)	.149	45	.013	.878	45	.000
CAI	.166	45	.003	.881	45	.000
血沉	.281	45	.000	.710	45	.000
C反应蛋白	.299	45	.000	.547	45	.000
降钙素	.344	45	.000	.553	45	.000

a. Lilliefors Significance Correction

**Comment 3:** Authors should explain where the Bonferroni adjustment was applied (usually as post-hoc test in the case of gaussian data)

**Response:** Indeed, we are very sorry for missing the interpretation of this and we add it in Statistical analyses section to make it clear. For Bonferroni adjustment, we divide the p-value for determining significance (0.05) by six and three, respectively, in multiple testing of noninvasive evaluations according to endoscopic activity grade (inactive/mild/moderate/severe) and correlations of parameters with disease location (L1/L2/L3 or E1/E2/E3) in CD and UC patients. For details please see Table3, Table3 and supplementary table2.

**Comment 4:** In the statistical analysis section it should be detailed about the variables used in the two multivariate models. Moreover, multiple linear regression models should be summarized in a table showing the coefficients. The complex scores for CD and CD should be explained in detail.

**Response:** This comment is valuable as it make the article more precise and explicit.

The regression equation of CFA was build with multiple stepwise regression analysis with FC, CDAI/CAI, CRP, ESR and PCT as independent variables. The coefficients of multiple linear regression models with Stepwise to construct CFA were showed in Supplementary Table 3.

	CICD patients		UC patients	
Model	Coefficients	Sig.	Coefficients	Sig.
Constant	-1.410		1.800	
FC	0.008	0.000	0.002	0.001
CDAI/CAI	0.046	0.001	0.501	0.002

What's more, the complex scores for CD and UC were explained on Page22 in detail.

**Comment 5:** No data about IBS patients were cited in the text.

**Response:** We are sorry for missing the interpretation of IBS patients in the text. In our study, IBS patients were served as control, our data also confirmed earlier findings that FC was able to differentiate IBD from IBS. Indeed, IBS patients still had significantly lower levels of FC when compared with endoscopic remission IBD patients. For details, please see first and second paragraph of discussion section(Page20 and Page22).

**Comment 6:** All ROC curves should be showed as supplementary material.

**Response:** Thank you for your kind comments. ROC curves for noninvasive markers levels in CD and UC patients: endoscopic active versus endoscopic remission were provided in Supplementary Figure1.

**Comment 7:** Reference 11 and 15 are the same.

**Response:** Thanks very much for your guidance. After careful checking, we found this mistake due to our careless and negligence. We also updated the format of all the references according to the Format for references guidelines.

**Response to editor Comments:**

We also provided all required documents that have to submit. We also carefully reviewed and corrected the grammatical errors throughout the paper. Additionally, we sent the paper to the Testcheck a company that provide a special online scientific and technical editing service and emailed our paper to Allen, a native English speaker, for modification of the writing style.