Answers to reviewers' comments

Reviewer #1:

Comment# 1:The research was to assess CDAI, CRP and Fcal variation, alone or combined, after 12 weeks (W12) of anti-TNF therapy to predict corticosteroids-free remission (CFREM= CDAI<150, CRP<2.9 mg/L and Fcal<250μg/g with no therapeutic intensification and no surgery) at W52. The research topic is innovative, the theoretical basis is solid, the experimental data is reliable, the statistical method is correct, the proof is sufficient, the conclusion is basically credible, the writing of the thesis is more rigorous, and the language expression is accurate. The research results have certain theoretical significance and clinical application value.

Answer #1: We thank reviewer #1 for his/her encouraging comment.

Comment# 2: The inadequacies and suggestions of the thesis: 1. What is the relationship between CDAI, CRP and Fcal variation and clinical and endoscopic remission?

Answer #2: Unfortunately, our study did not include systematic endoscopic evaluation. Then, we are not able to provide these data.

Comment# 3: 2. CDAI, CRP and Fcal variation of CD was observed in 12 and 52 weeks. Why isn't it observed in 24 or 30 weeks?

Answer #3: Our design did not include systematic clinical evaluation at week 24 or week 30.

Reviewer #2:

Comment# 4: Sollelis E et al (Manuscript Number: 47053) describe and evaluate the "Combined evaluation of biomarkers as predictor of maintained remission in Crohn's disease". The observation and analysis objects of this work including assessment of "the performances of CDAI, CRP and faecal calprotectin Fcal variation, alone or combined, after 12 weeks of anti-TNF therapy to predict corticosteroids-free remission (CFREM) at one year, in CD patients treated with anti-TNF." Findings of this prospective study are "The combined monitoring of CDAI, CRP and Fcal after anti-TNF induction therapy is able to predict favorable outcome within one year in patients with CD." It is a tough issue to treatment the Crohn's disease (CD) and difficulty to obtain a long-lasting corticosteroid (CS)-free disease remission with a good quality of life. Hence, this work reported here is interesting. This study further confirms the conclusions of "CDAI, CRP and Fcal could be used as predictor of maintained remission in Crohn's disease, and Fcal was the most effective predictor among these three markers." 1. The quality

of logic and presentation of the key idea, statistical analysis and discussion are good. 2. The content of the article is corresponding well to the title.

Answer #4: We thank reviewer #2 for his/her encouraging comment.

Comment# 5: The value of the statistical analysis should be written in the corresponding graphs and tables. 4. The Table, Figure, Reference, and special symbols must fit the journal's requirements or format.

Answer #5: We thank reviewer #2. We took into account his/her comment to improve the revised manuscript.

Reviewer #3:

Comment# 6: These authors have tackled the ingenious job of determining which individual indicator or combination of indicators in a "package" of three markers, measured at 12 weeks of anti-TNF therapy, best predicts steroid-free remission at one year. Combined assay of all three markers seemed to do well, with FCal evidently the best performing of the individual factors.

Answer #6: We thank reviewer#6 for his/her encouraging comment.

Comment# 7: It would be helpful if the authors could address three particular points: Is it valid to do an assessment of the predictive value of the same three "predictors" that constitute the definition of the endpoint (CFREM)?

Answer #7: It's a good point. We considered that achieving normalization of clinical symptoms, of CRP value and faecal calprotectin level is a reference standard due to the results of the CALM trial (Colombel *et al.* Lancet 2018). We assessed the performances of each biomarker alone or combined *i.e.* CDAI, CRP and faecal calprotectin to predict what we believe the best definition of steroids-free remission according to the CALM definition. We considered that our data added meaningful information on the need to assess routinely CDAI or CRP besides calprotectin.

Comment# 8: 2. Has there been any effort to apply this analysis to a validation cohort, enrolled prospectively or at least elsewhere?

Answer #8: I would have been interesting but would need to perform a second study.

Comment# 9: 3. Has there been any test of heterogeneity among the three participating centers?

Answer #9: **Yes, we did, and we did not observe any heterogeneity among the three centers. However, due to the relatively small number of patients in our study, we decided to not include it in the manuscript.**

Comment# 10: I also note that the Abstract does not state the same conclusion as the text.

Answer #10: **I respectfully disagree with reviewer#3. I don't think the conclusions are different. The conclusion of the abstract was "The combined monitoring of CDAI, CRP and Fcal after anti-TNF induction therapy is able to predict favorable outcome within one year in patients with CD" while the conclusion of the article was "In conclusion, the combined monitoring of CDAI, CRP and FCal after anti-TNF induction therapy is able to predict favorable outcome within one year in patients with CD. The most impactful biomarker was Fcal among these three biomarkers. Our results should lead IBD physicians to monitor patients with CD using a tight control strategy based on CDAI, CRP and Fcal in daily practice." The conclusion of the abstract was less detailed due to the restricted number of words.**