Reviewer #1:
Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)

Specific Comments to Authors:
The researchers discovered that GDF-15 exhibits potential as a prognostic indicator for unfavorable outcomes in individuals with inflammatory bowel disease (IBD), thereby possessing notable clinical implications. There are several issues in this paper that need to be explained. Further modifications are recommended.

Response: Dear Reviewer, thank you for taking time in reviewing our manuscript. We hope that, upon applying the request changes, our manuscript will be ready for publication in WJG.

1.The electrochemiluminescence immunoassay is primarily appropriate for detecting small molecules, while its application for large molecules like proteins is limited due to the potential for false positive results. This article aims to elucidate the rationale behind selecting this method for GDF-15 detection and whether there is any existing literature supporting this choice.

Response: Dear Reviewer, thank you for valuable comment. Nonetheless, the GDF-15 kit used in this study (The Elecsys GDF-15) has been extensively tested for possible interference. Specifically, we hereby attach the snippet of this analysis performed by the manufacturer as a proof.

Limitations - interference
The effect of the following endogenous substances and pharmaceutical compounds on assay performance was tested. Interferences were tested up to the listed concentrations and no impact on results was observed.

Endogenous substances

Compound	Concentration tested
Bilirubin	≤ 1129 µmol/L or ≤ 66 mg/dL
Hemoglobin	≤ 0.621 mmol/L or ≤ 1000 mg/dL
Intralipid	≤ 2000 mg/dL
Biotin	≤ 205 nmol/L or ≤ 50 ng/mL
Rheumatoid factors	≤ 1200 IU/mL

Compound	Concentration tested
IgG	≤ 55 g/L
IgM	≤ 10 g/L
IgA	≤ 13 g/L
Albumin	≤ 70 g/L

Criterion: Recovery within ± 80 pg/mL for GDF-15 concentrations ≤ 800 pg/mL or ± 10 % for concentrations > 800-2000 pg/mL or ± 14 % for concentrations > 2000 pg/mL of initial value.

Samples should not be taken from patients receiving therapy with high biotin doses (i.e. > 5 mg/day) until at least 8 hours following the last biotin administration.

There is no high-dose hook effect at GDF-15 concentrations up to 150000 pg/mL.

Pharmaceutical substances
In vitro tests were performed on 16 commonly used pharmaceuticals. No interference with the assay was found.

In addition, the following special cardiac drugs were tested. No interference with the assay was found.

2.Whether the reason for the higher concentration of GDF-15 in the serum of IBD patients than that in the healthy control group can be further explained. Furthermore, what prevents us from accurately predicting the occurrence of Crohn's disease (CD) and ulcerative colitis (UC)?

Response: Dear Reviewer, thank you for valuable comment. First of all, it is important to disclose that in the absence of data concerning the role of GDF-15 in IBD, we can only hypothesize about its implications in this disease. Nonetheless, we endeavored to use contemporary data about GDF-15 in related disorders and associate it with our findings. Specifically, we hypothesized that

elevated GDF-15 reflects its protective role in this inflammatory disorder. The data supporting this notion can be found in preclinical studies with GDF-15 deficient mice, in which lack of GDF-15 was associated with more pronounced systemic (increased levels of IL-6, IL-12, TNF-α, and IFN-γ in the serum) and local inflammatory response (increased T-cell infiltration and CXCR3 upregulation). The interpretation is further complicated by the presence of anemia (which is by itself challenging in IBD, pathophysiologically speaking, because of the overlap of iron-deficiency and chronic disease anemia mechanisms). Specifically, GDF-15 was associated negatively associated with anemia indices in our study, but owing to disputed association of GDF-15 and hepcidin it is hard to make solid conclusions on whether GDF-15 levels are higher because of iron-loss or the underlying inflammatory processes. Concerning the lack of difference between CD and UC we hypothesize that GDF-15 may be elevated in both instances owing to some of the various overlapping chronic inflammatory pathways between CD and UC. We have now expanded our discussion with these notions.

3.Compared with the gold standard for clinical prediction of IBD, what are the advantages of detecting GDF-15?

Response: Dear Reviewer, thank you for valuable comment. Reliable long-term prognostic indicators in IBD are scarce and therefore we think that this area of research has significant potential. Specifically, the authors believe that increased GDF-15 levels might be a proxy for poor outcomes owing to the fact that it was associated with very reliable indicators of disease severity (SES-CD and UCEIS, respectively) independently of the CRP levels. Moreover, as GDF-15 levels were shown to predict cardiovascular outcomes very well, we believe that GDF-15 will to some extent explain the paradoxical worse cardiovascular outcomes in these patients (i.e., less traditional risk factors but worse CVD outcomes). We have now expanded the discussion with these notions.