

## Format for ANSWERING REVIEWERS

March 7, 2017

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 31329-review.doc).

**Title:** Impact of vitamin D on the hospitalization rate of Crohn's disease patients seen at a tertiary care center

**Author:** Krishna VR Venkata, Sumant S Arora, Feng-Long Xie, Talha A Malik

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 31329

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Dear Editors of World Journal of Gastroenterology,

Thank you for reviewing our manuscript and providing insightful edits. This letter serves as the point-by-point reply to each of the suggested edits. Edits are also highlighted in the revised manuscript. We hope we have addressed all of the reviewers' comments in a thorough way while still addressing the key findings of this study. Furthermore, we welcome any further edits to ensure we produce an exceptional publication that readers will find educational and beneficial.

Thank you,

Krishna VR Venkata, MD

Point-by-point reply appended below:

## COMMENTS FOR THE AUTHOR:

### Reviewer # 1: World Journal of Gastroenterology

Interesting topic, however authors listed few causes of vit.D deficiency but only one mentioned, while describing their own results. Seems to might be interesting to provide such research in patients with ulcerative colitis

Reply: Thank you for your comments.

a) Several factors have been shown to predict vitamin D deficiency in CD. These include: insufficient sunlight exposure, malnutrition, impaired conversion of vitamin D to metabolite (i.e. 25-hydroxycholecalciferol), accelerated breakdown, heightened excretion, and gene mutations affecting vitamin D hydroxylation and transport. The following line was added in the discussion section. "Retrospective observational study design and the use of electronic medical records (EMR) for data extraction are additional limitations. Due to this limitation, we couldn't accurately assess the various causes associated with vitamin D deficiency in our patient population".

b) We are currently doing similar kind of retrospective study in patients with ulcerative colitis.

### Reviewer #2: World Journal of Gastroenterology

I'm pleased to review the precious paper entitled "Impact of Vitamin D on the Hospitalization Rate of Crohn's Disease Patients Seen at a Tertiary Care Center". The authors investigated the association between Vitamin D level and the Hospitalization Rate in Crohn's Disease Patients seen at a Tertiary Care Center in a retrospective cohort study and found that CD patients with a low mean vitamin D level were more likely to be admitted compared to those with an appropriate vitamin D level.

Major points A review published in 2014 described that vitamin D deficiency was associated with increased risk of hospitalizations in CD (OR 2.1, 95% CI 1.6 – 2.7) 1). A meta-analysis on the association between vitamin D and CD activity showed that there was an inverse correlation between circulating 25(OH)D concentrations and severity of CD 2). Expert Review have pointed out that the important question is whether interventions to raise 25OHD levels would modify disease activity or not 3). Please clearly explain the term "Tertiary Care", the meaning of "unique" and the distinct difference of this paper from previous ones. Ref 1. Mouli VP, Ananthakrishnan AN. Review article: vitamin D and inflammatory bowel diseases. Aliment Pharmacol Ther. 2014;39(2):125-36. doi: 10.1111/apt.12553. 2. Sadeghian M1, Saneei P1, Siassi F2, Esmailzadeh A3. Vitamin D status in relation to Crohn's disease: Meta-analysis of observational studies. Nutrition. 2016 ;32(5):505-14. 3. O'Sullivan M. Is vitamin D supplementation a viable treatment for Crohn's disease? Gastroenterol Hepatol. 2016;10(1):1-4.

Reply: Thank you for your comments

1) The following line is added to the discussion (last paragraph, first sentence). While previous papers studied association between vitamin D and Crohns disease but out study is unique as the first time discussing hospitalization rate

2) The following line is added to the discussion (last paragraph,, 5<sup>th</sup> sentence). Further studies need to be done to assess if interventions to raise Vitamin D level will decrease hospitalization rates.

3) The following line is added to the introduction (5<sup>th</sup> paragraph) to explain “tertiary care” and “unique”

“University of Alabama at Birmingham (UAB) is the only tertiary care IBD referral center in the state of Alabama that provides health care by dedicated sub-specialists in a large hospital with sophisticated intensive care facilities after referral from primary care and smaller hospitals. IBD center had facilities available for both inpatient and outpatient management of patients with Crohn’s disease and its complications and so it is a unique setting to study the effect of various covariates such as vitamin D levels on outcomes in CD. ”

#### Minor points

1) Please explain the reason the author used the threshold of 30 ng/ml. Some papers used 20 ng/ml as a Vitamin D level. 4) Ref 4. A.N. Ananthakrishnan, A. Cagan, V.S. Gainer, T. Cai, S.C. Cheng, G. Savova, et al. Normalization of plasma 25-hydroxy vitamin D is associated with reduced risk of surgery in Crohn's disease. *Inflamm Bowel Dis*, 19 (2013), pp. 1921–1927

Reply: In our hospital, the laboratory reference value for the normal lower limit for Vitamin D level is 30ng/ml and so we used it as threshold. The following line is added to data collection and variable definitions. “We used 30ng/ml as threshold as it is the laboratory reference value for normal lower limit of vitamin D levels in our hospital.”

2) The meaning of "196 with vitamin D level" is vague. Vitamin D level was measured in 196 out of all 880 patients?

Reply: Corrected as recommended and new line is added to the results section. “Vitamin D levels were measured in 196 out of 880 CD patients seen at our institute during the observation period and were included in this study.”

3) Page 3,Introduction Line 8, The authors described “However, whether vitamin D deficiency contributes as a risk factor for CD or affects CD outcomes, remains unclear [23,32]”. As described at major point, a review published in 2014 and a meta-analysis published in 2016 have described the association between vitamin D deficiency and increased risk of hospitalizations or Disease activity in CD.

Reply: Thank you for your comment. We removed the line from the introduction as suggested by reviewer.

3) Page 5, Data Collection and Variable Definitions, Line 2. Please spell out EMR at first time (EMR was spelled out at the second time).

Reply: EMR was spelled out as Electronic medical records in the Data Collection and Variable definitions sections;

4) Page 7, Line 5. "Our findings could have few plausible interpretations." "a few" is correct?

Reply: corrected as recommended

5) Please indicate the basic policy to measure vitamin D level in the center for both outpatients and inpatients.

Reply: Thank you for your comment. At our tertiary care center, vitamin D level is measured routinely at baseline initially in outpatient setting including our IBD clinic.

Reviewer #3: World journal of gastroenterology

This is a well-written manuscript on impact of adequate levels of Vit-D on hospitalization rates in patients with CD. The study is observational, based on retrospective chart review. In my opinion there are no major modifications needed.

Reply: Thank you for your comment.