Dear Editors and Reviewers:

We would like to thank the editor and the reviewers for their conscientious reviews, and insightful comments and suggestions to improve our manuscript entitled "**Mucosal lesions of the upper gastrointestinal tract in patients with ulcerative colitis: A review**" (**Manuscript NO.: 63662**). All the comments are valued, professional and helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied the comments carefully and have made corrections which we hope meet with approval. We would like to re-submit this revised manuscript and hope it is acceptable for publication in ***World Journal of Gastroenterology***. Please do not hesitate to contact us with any additional questions or concerns. The main corrections in the paper and the responds to the reviewer's comments are as following:

Reviewer #1:

Scientific Quality: Grade B (Very good)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor revision
Specific Comments to Authors: The authors wrote a generally good review on upper GI lesions in ulcerative colitis. This is, overall, of very high interest. Following points should be improved. There are many environmental, dietary, and lifestyle factors that influence the microbiome (in both intestinal lumen and tissue), immune system, pathogenic mechanisms. Upper and lower GI are connected and may have related pathogens. The authors should discuss these points; influence of those factors, eg, smoking, alcohol, diet, obesity, microbiome, immunity. There are also influences of germline genetic variations on both immune system and microbiota. Gene-by-environment interactions should be discussed. In these contexts, as a future direction, research on dietary/lifestyle factors, microbiome, immunity, and personalized molecular biomarkers in these diseases is needed. The authors should discuss molecular pathological epidemiology (MPE), which can investigate those

factors in relation to molecular pathologies, immunity, and clinical outcomes. MPE research can be a promising direction and improve prediction of response to pharmacological, dietary, and lifestyle intervention. MPE and its strengths/challenges discussed in Epidemiology 2016, Annu Rev Pathol 2019, etc. should be discussed in this paper.

Response: We really appreciate your constructive suggestion. According to your kindest suggestion, we have added the information about the pathogenesis of ulcerative colitis, including environmental and host factors, genetic variants, gut microbiota and immune system. Moreover, we read the papers the reviewer's recommended to us, and we found they were very helpful and insightful to improve our paper. We cited them and discussed in the corresponding parts. The description was listed as following:

PATHOGENESIS OF UC

It is believed that UC may be mainly determined by a complex combination of environmental and host factors, genetic variations, immune response and gut microbiota. The onset of this disease is activated by disturbance of the mucosal barrier, gut microbiota, and abnormal immune response. Many scholars support that the abnormal immune response (innate and adaptive) is a key direct pathogenesis, in which gut microbiota is an important stimulus for this immune damage process and the environmental and host factors may be the causative factors of the disease.

Environmental and host factors

It has been well acknowledged that the environmental and host factors play critical roles in increasing the susceptibility of developing UC. The increasing incidence of UC worldwide implies the significance of environmental factors in the progression of this disease [86, 87]. This is similar to the pattern detected in the Western world in the early 20th century [88]. UC has been specifically occurred in urban zones, and its incidence is faster and then slower. Westernization and its accompanying urbanization, sedentary lifestyle, exposure to environmental pollution, dietary changes, antibiotics usage, refrigeration, better sanitation and fewer infections, all of which are regarded as contributing factors [89]. For example, former cigarette smoking has been reported

as one of the UC strongest risk factors, whereas compared to the former and non-smokers, active smokers are less probably to suffer from UC and they mainly present with a milder clinical course [90-92]. Furthermore, appendectomy is considered as a protective impact on future developing UC [93].

Genetic variants

Genetic studies have been predominantly effective in recognizing both common and infrequent genetic variants susceptibility loci associated with UC [94-96]. Human leukocyte antigen (HLA) [97] and adenylate cyclase type 7 (ADCY7) [98] are the two important UC-specific genes. Moreover, many UC-specific genes are confirmed to be responsible for mediation of epithelial barrier function. However, it has been established that UC and CD shared most genetic factors. These shared genetic factors could encode cytokine, innate and adaptive immune signal pathways, and immune sensing, such as interleukin (IL)-10, -12, -23R, and caspase recruitment domain containing protein 9 (CARD9). In addition, it has been demonstrated that about 70% of genetic variants are also commonly seen in some other autoimmune diseases, such as ankylosing spondylitis and psoriasis [86]. Overall, genetic factors deliberate a small but certain increase in susceptibility to UC. Nevertheless, many individuals who do not present with genetic susceptibility, accounting for all susceptibility loci when evaluated by polygenic risk scores [99]. These findings imply that an abnormal adaptive immune response and epithelial barrier dysfunction may play critical roles in the pathogenesis of UC.

Gut microbiota

A series of animal experiments and clinical trials have confirmed the presence of significant intestinal flora dysbiosis in patients with UC [100, 101]. The dysbiosis of intestinal flora is featured by decreased biodiversity, irregular composition of gut microbiota, changes of spatial distribution, together with interactions between microbiota and the host [101]. There is a significant change in the number of intestinal bacteria in patients with UC, which is reflected in a decrease in probiotic bacteria (e.g. Bifidobacterium and lactobacillus, etc.) and an increase in conditionally pathogenic bacteria (such as Enterococci and Enterobacteria, etc.). Therefore, an increasing

studies pay attention on the therapeutical effects of faecal microbial transplantation (FMT) from healthy donors on patients with UC [100, 102-105].

Immune system

UC is a pathogenic inflammatory disease mediated by the immune system including innate immunity and adaptive immunity [106]. The innate immunity is the first line of defense against pathogens. Unlike adaptive immunity, innate immunity is non-specific and persistent. Immune cells in innate immunity, such as dendritic cells (DCs), macrophages, natural killer (NK) cells, intestinal epithelial cells and myofibroblasts, can sense the intestinal microbiota and respond to conserved structural motifs of microorganisms, which can trigger a rapid and effective inflammatory response and prevent bacterial invasion[107]. Among them, DCs are specialized antigen-presenting cells responsible for T-cell activation and induction of adaptive immune responses and they are key players in the interplay between innate and adaptive immunity [107]. For the adaptive immune system, the components of this system cooperate with each other, with the molecules, and with the cells in the innate immune system to mount an effective immune response that eliminates invading pathogens under normal conditions. Unlike innate immunity, adaptive immunity has highly specific long-term immunity and is adaptive because antigen specificity is the result of complex maturation and development of immune cells. T helper (Th) cells are key elements to the adaptive immune response. UC is mainly activated by Th2 cells-induced immune response [108]. Th2 cells are mainly induced by IL-13 and then subsequently secrete IL-4, IL-5, and IL-13, in which IL-13 is considered as to be essential to the pathogenesis of UC [109].

MOLECULAR PATHOLOGICAL EPIDEMIOLOGY (MPE)

MPE has been reported as an integrative transdisciplinary science, which integrates the academic disciplines of molecular pathology and epidemiology [115-118]. Unlike conventional epidemiologic research, such as genome-wide association studies (GWAS), MPE mainly figures out the underlying heterogeneity of disease processes, whereas traditional molecular epidemiology typically treats a disease as an individual

entity [119, 120]. Similar to the biology systems and WebMed [121, 122], MPE combines the analysis of overall populations and macroenvironments, which is involved in the molecular analysis and microenvironments. In addition, the goal of MPE is to explore the mutual relation between exogenous and endogenous elements, molecular markers and progression of malignancy [118, 123, 124]. More importantly, MPE research could cover all human diseases. Therefore, MPE studies can offer insightful aspects on the pathogenesis of disease by validating specific mechanisms in disease development and progression [123].

It has been well demonstrated that traditional epidemiology investigation reveals many factors, such as lifestyle, dietary, and environmental exposures, could be positively or negatively related with risk of illness [118, 125]. Nevertheless, it is still unclear how these exposures impact the disease pathogenesis. Previous studies have confirmed that these above factors probably affect the pathogenic process by changing the local tissue microenvironment, and epigenetics play an important role in cellular response to alterations in the microenvironment [115]. An increasing number of evidence demonstrates application of MPE in colorectal cancer research to find out the possible etiologic factors [126-130]. Nonetheless, little information is available with respect to the research of MPE on UC. UC has been considered as a heterogeneous disease, in which smoking, alcohol, diet, obesity, microbiome, inflammation, immunity, germline genetic variations and gene-by-environment interactions are responsible for the progression of UC [131, 132]. Therefore, MPE may be helpful to investigate those factors in relation to molecular pathologies, immunity, and clinical outcomes.

Though the MPE research has a lot of advantages, the challenges should also be taken into consideration. Primarily, the reported challenges in the MPE study comprise the selected sample size, requirement for severe corroboration of molecular examines and study discoveries, lack of multidisciplinary experts, international forums, as well as the standardized strategies [120]. Furthermore, MPE studies have to confront the problem of various hypothesis challenging and therefore require the formation of a priori hypotheses on the basis of early exploratory discoveries or possible biological

mechanisms [118]. Moreover, MPE may also generate more opportunities for false discoveries [120]. In consideration of the pathogenesis of UC, MPE paradigm may be a promising direction and improve prediction of response to pharmacological, dietary, and lifestyle intervention for UC, together with the pathomechanism and treatment of mucosal lesions of the UGI tract in patients with UC.

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We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. Once again, we sincerely appreciate for reviewers' warm work, and hope that the revision is acceptable and look forward to hearing from you soon.

With best wishes,

Dr. Sang