Penn Medicine
Perelman School of Medicine
University of Pennsylvania Health System

Rotonya Carr, MD
Assistant Professor of Medicine

Department of Medicine
Division of Gastroenterology

October 27, 2020

Dear Editor:

We are appreciative of the insightful critiques provided by the reviewer. The revised manuscript has been modified substantially to strengthen this review and address the reviewer's comments. In particular, we modified the organization to make it more intuitive and added different animal models of non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) as suggested. Below are the specific responses to the reviewers' critiques:

Reviewer 1:

Experimental model plays an important role in the study of metabolic and alcoholic fatty liver disease. The topic of this review is interesting and has clinical significance. However, the article introduces the animal model of fatty liver, but the article does not follow different models how to establish? *Thank you for your review and commendation. We added a description regarding the animal models of NAFLD and ALD, and then moved on to discussing the established animal models of SMASH in detail.*

What are the signs of success? What's the difference with the actual fatty liver patients? *Thank you for your review and commendation. As suggested, we added further discussion in the conclusion of the pathological features seen in fatty liver patients that would make a successful SMASH animal model. We also discussed both advantages and disadvantages of the reviewed animal models with regards to their ability to model pathology in actual fatty liver patients.*

It is suggested to make a major revision, which can be stratified according to different modeling methods, such as alcoholic fatty liver and non-alcoholic fatty liver, and then compare their similarities and differences of clinical and pathological features, and put forward the establishment method of metabolic alcoholic fatty liver model. *Thank you for your review and suggestion of an improved structure for the paper. As suggested, we created a section called "II. Pathological overlap between NAFLD and ALD" that describes the pathological overlap between NAFLD and ALD, including lipid dysregulation, oxidative stress, immune response, apoptosis, and fibrosis. We also created a section called "III. Experimental models of NAFLD and ALD, in which we describe currently established rodent models for NAFLD and ALD. We then introduce the review of experimental models of metabolic alcoholic fatty liver disease in the section entitled "IV. Experimental models of SMASH". This section of the review has two subsections "Dietary models of SMASH" and "Genetic models of SMASH". In each subsection, we describe published models of metabolic alcoholic fatty liver disease and compared their ability to recapitulate the NAFLD-ALD overlap condition described in Section II.*

We hope that these improvements to our manuscript are received favorably and look forward to your decision.

Sincerely,

Rotonya M. Carr, MD
Assistant Professor of Medicine
Division of Gastroenterology
University of Pennsylvania

907 Biomedical Research Building II/III • 421 Curie Boulevard • Philadelphia, PA 19104-4863
Phone: 215-349-8222• Fax: 215-573-2024 • Email: Rotonya.Carr@uphs.upenn.edu