

Reviewer Report

Title: Analysis of SARS-CoV-2 known and novel subgenomic mRNAs in cell culture, animal model and clinical samples using LeTRS, a bioinformatic tool to identify unique sequence identifiers.

Version: Revision 1 **Date:** 12/13/2021

Reviewer name: Chan Zhou

Reviewer Comments to Author:

Comments: It is an important study. Except for a few minor points, the authors have addressed most of the reviewers' suggestions. This manuscript will be considered for acceptance after addressing the following minor suggestions:

1. The authors have compared the algorithm design, input, and output, and the counts of predicted sgmRNA across four tools. However, it would be nice if the authors could compare these tools' performances regarding prediction accuracy, F-measure, sensitivity, and specific scores. These will let the readers and potential users have a better sense of choosing a different tool for different purposes.
2. It is unclear what the red line means in Supplemental Figure 8-9.
3. On page 18, lines 364-370. The analysis and significance that the authors stated in that paragraph do not show the apparent trends in Supplemental Figure 9. Would the authors update the figure types to reflect the results of their statistical tests?
4. On page 18, line 370. The author mentioned that "The abundance of most sgmRNAs decreased with time, and both of these factors could account for the frequency of methylation." Based on the context, it seems that the conclusion could not be derived. Because the methylation frequency is a ratio, then it may not correlate with the abundance of the sgmRNAs.

Methods

Are the methods appropriate to the aims of the study, are they well described, and are necessary controls included? Choose an item.

Conclusions

Are the conclusions adequately supported by the data shown? Choose an item.

Reporting Standards

Does the manuscript adhere to the journal's guidelines on [minimum standards of reporting?](#) Choose an item.

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