Review 1: "A rigorous framework for detecting SARS-CoV-2 spike protein mutational ensemble from genomic and structural features "

Dalal Harkati¹

¹Universite Mohamed Khider de Biskra, Matter sciences, Algeria

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RR:C19 Evidence Scale rating by reviewer:

- **Strong.** The main study claims are very well-justified by the data and analytic methods used. There is little room for doubt that the study produced has very similar results and conclusions as compared with the hypothetical ideal study. The study's main claims should be considered conclusive and actionable without reservation.

Review:

I have been through the manuscript entitled "A rigorous framework for detecting SARSCoV-2 spike protein mutational ensemble from genomic and structural features" which is tracking 3,11,795 genome sequences of spike protein which comprises 2,584 protein mutations. The interesting finding in this manuscript is the detection of three novel mutational clusters, namely A222, N439, and S477. However, there are a few minor comments I would like to add: The resolution of the images should be increased. The manuscript in general is strong. I recommend that the paper is suitable for publication in Rapid Reviews: COVID-19.