Review 2: "Non-invasive Vagus Nerve Stimulation for Respiratory Symptoms of COVID-19: Results From a Randomized Controlled Trial (SAVIOR I)"

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RR:C19 Evidence Scale rating by reviewer:

- **Reliable.** The main study claims are generally justified by its methods and data. The results and conclusions are likely to be similar to the hypothetical ideal study. There are some minor caveats or limitations, but they would/do not change the major claims of the study. The study provides sufficient strength of evidence on its own that its main claims should be considered actionable, with some room for future revision.

Review:

The strength of evidence of this study is reliable.

Firstly, the evidence is reliable due to the method used: randomized and controlled trial. The control group is of particular importance. The study lasted almost one year, allowing rapid evolution of the clinical standards of care for COVID-19 with a significant impact on the inflammation markers by itself (glucocorticoids, antivirals, monoclonal antibodies...). Moreover, although there was no stratification of the study population, randomization (small but sufficient with 97 patients enrolled) allowed for similar baseline characteristics between the two arms. (The mean participant age was only six years higher in the SoC group than in the nVNS group, respectively 55.5 and 61.3 years old. Males represented roughly 70% in both arms, smoking status and comorbidities were similar in both groups).

Secondly, the results and conclusion are likely to be similar to the hypothetical, ideal study because two validated inflammatory biomarkers (CRP and procalcitonin) were significantly reduced in the nVNS group. Besides, the efficacy of nVNS is assessed on a short but suitable period (only five days). COVID-19 patients are known to undergo respiratory failure rapidly, within a few days and sometimes within a few hours after hospital admission.

However, this study has some minor limitations: it is a monocentric study, enrolling a small population without assessing the long-term outcomes. In addition, considering that a pandemic is very challenging for consistent data collection, Heart rate variability monitoring should be considered in the ongoing trial SAVIOR II or the next one.

At last, this manuscript contributes to broader research understanding (how to reduce the cytokine storm and improve respiratory symptoms of COVID-19) and supports the advancement of ambulatory non-invasive therapeutics. Thus, paying attention to ethics, diversity, and inclusion. Therefore, I would recommend this manuscript for publishing, provided the authors include a more detailed discussion of the limitations and a better positioning within the current literature.