Review 1: "Serum Sphingosine-1-Phosphate as Novel Prognostic and Predictive Biomarker for COVID-19 Severity and Morbidity and Its Implications in Clinical Management"

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RR:C19 Evidence Scale rating by reviewer:

- **Potentially informative.** The main claims made are not strongly justified by the methods and data, but may yield some insight. The results and conclusions of the study may resemble those from the hypothetical ideal study, but there is substantial room for doubt. Decision-makers should consider this evidence only with a thorough understanding of its weaknesses, alongside other evidence and theory. Decision-makers should not consider this actionable, unless the weaknesses are clearly understood and there is other theory and evidence to further support it.

Review:

This manuscript by Giovanni Marfia et al. reports the clear-cut data showing that serum levels of sphingosine-1-phosphate (S1P), a blood-borne multi-functional lipid mediator, were reduced in COVID-19 patients compared with age- and sex-matched healthy subjects and that the decrease in serum S1P was correlated with decreases in blood levels of erythrocyte, apoM, which is an HDL-associated apo protein, and albumin. Erythrocytes are major producers of blood S1P, whereas apoM and albumin are major S1P carrier proteins in blood. The reductions of serum S1P, as well as erythrocytes, apoM and albumin, were more severe in ICU-admitted COVID-19 patients compared with non-ICU-admitted COVID-19 patients. Further, serum S1P level was a significant predictor for ICU admission and in-hospital mortality. Collectively, the authors suggest circulating S1P levels as negative biomarker, which is clinically useful for predicting COVID-19 patient's outcome.

In this manuscript, the authors reasonably discussed two points, (1) mechanisms underlying the reduction of serum S1P and (2) pathological consequences and clinical implications of reduced serum S1P. Regarding the first point, the authors suggested that the decreased erythrocytes in blood resulted in reduced S1P release into plasma from erythrocytes and that the decreased apoM and albumin, both of which were downregulated as negatively regulated acute phase proteins during the inflammatory condition, also contributed to the reduced serum S1P level. Regarding the second point, they suggested that S1P may play a role in inflammation and immune responses in COVID-19 patients because S1P plays crucial pathophysiological roles particularly in the maintenance of vascular barrier function and lymphocyte traffics between blood

In general, this manuscript is presenting the interesting data of reduced S1P levels in COVID-19 patients and their correlation with severity of COVID-19. The manuscript is well-written and the interpretation of the data is sound.

The critique by this reviewer includes:

- (1) Is a reduced serum S1P level a biomarker specific for COVID-19 patients or rather common for other viral infections, bacterial infections and non-infectious inflammatory diseases which are accompanied by decreased blood erythrocytes and albumin?
- (2) Could an approximately 20% reduction (as the median value) of serum S1P observed in COVID-19 patients be involved in the pathophysiology of COVID-19 by exerting significant modulatory influences on vascular barrier function and immune cell responses in the face of the presence of a large blood S1P pool as HDL- and albumin-bound forms?
- (3) Is the authors' suggestion that "restoring S1P abnormal levels to a normal range, and balancing its binding to albumin and apoM to physiological conditions, may represent a potential therapeutic strategy---" (bottom four lines in page 3) supported sufficiently by the present data?