RAGE has potential pathogenetic and prognostic value in non-intubated hospitalized patients with COVID-19

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Supplemental Methods:

Inclusion and exclusion criteria

Patients were eligible for the ACTIV-3/TICO LY-CoV555 trial if they were 18 years of age, had a positive PCR or other nucleic acid test for SARS-CoV-2 more than 3 days prior to randomization and progressive symptoms suggestive of ongoing infection, symptom duration 12 days, and required hospitalization for COVID-19 and NOT for public health or quarantine purposes. Subjects were excluded if they: had previously received any SARS-CoV-2 hyperimmune intravenous immunoglobulin, convalescent plasma from person who recovered from COVID-19, or any SARS-CoV-2 monoclonal antibody prior to hospitalization; were unwilling to forego other COVID-19 treatment trials until after day 5; had a condition for which, in the opinion of the responsible investigator, would not be in the best interest of the patient or would limit protocol-specific assessments; were expected to be unable to participate in study procedures; or were of child-bearing potential or a partner of someone of childbearing potential and were unable or unwilling to either abstain from sexual intercourse or use appropriate contraception. Subjects were also excluded if any of the following were present at enrollment (stage 1 only):

- stroke
- meningitis
- encephalitis
- myelitis
- myocardial infarction
- myocarditis
- pericarditis
- symptomatic congestive heart failure (NYHA class III-IV) i. arterial or deep venous thrombosis or pulmonary embolism

Or if there were current or imminent requirement for any of the following (stage 1 only):

- invasive mechanical ventilation
- ECMO
- mechanical circulatory support
- vasopressor therapy
- commencement of renal replacement therapy at this admission (i.e. not patients on chronic renal replacement therapy).

Outcomes

Day 5 Ordinal Outcomes

The 2 ordinal outcomes are assessed at day 5. The first ordinal outcome is a 7-category outcome largely based on oxygen requirements. The highest category that applies on day 5 was assigned. This outcome is referred to as the "pulmonary" ordinal outcome and is defined below:

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen)
5. Non-invasive ventilation or high-flow oxygen
6. Invasive ventilation, extracorporeal membrane oxygenation (ECMO), mechanical circulatory support, or new receipt of renal replacement therapy
7. Death

The second ordinal outcome, also assessed at Day 5, captures the range of organ dysfunction that may be associated with progression of Coronavirus-Induced Disease 2019

(COVID-19), such as respiratory dysfunction and coagulation-related complications. Again, the highest category that applies on day 5 was assigned. This outcome is referred to as the "pulmonary+" ordinal outcome. The 7 categories of the pulmonary+ ordinal outcome assessed at Day 5 are:

1. Can independently undertake usual activities with minimal or no symptoms
2. Symptomatic and currently unable to independently undertake usual activities but no need of supplemental oxygen (or not above premorbid requirements)
3. Supplemental oxygen (<4 liters/min, or <4 liters/min above premorbid requirements)
4. Supplemental oxygen (≥4 liters/min, or ≥4 liters/min above premorbid requirements, but not high-flow oxygen) or any of the following: stroke (NIH Stroke Scale [NIHSS] ≤14), meningitis, encephalitis, myelitis, myocardial infarction, myocarditis, pericarditis, new onset CHF NYHA class III or IV or worsening to class III or IV, arterial or deep venous thromboembolic events.
5. Non-invasive ventilation or high-flow oxygen, or signs and symptoms of an acute stroke (NIHSS >14)
6. Invasive ventilation, ECMO, mechanical circulatory support, vasopressor therapy, or new receipt of renal replacementtherapy
7. Death

The present study focuses on the pulmonary outcome since the results were similar across the two ordinal outcome definitions.

<u>Time from randomization to sustained recovery:</u>

The primary endpoint of the ACTIV-3/TICO LY-CoV555 trial was time from randomization to sustained recovery, where sustained recovery is defined as being discharged from the index hospitalization, followed by being alive and *home* for 14 consecutive days prior to Day 90. *Home* is defined as the level of residence or facility where the participant was residing prior to hospital admission leading to enrollment in this trial (the index hospitalization).

Residence or facility groupings to define home are:

1) **Independent/community dwelling** with or without help, including house, apartment, undomiciled/homeless, shelter, or hotel;

2) **Residential care facility** (e.g., assisted living facility, group home, other non-medical institutional setting); 3) **Other healthcare facility** (e.g., skilled nursing facility, acute rehab facility); and

4) L**ong-term acute care hospital** (hospital aimed at providing intensive, longer term acute care services, often for more than 28 days).

Lower (less intensive) level of residence or facility will also be considered as home. By definition, "home" cannot be a "short-term acute care" facility. Participants previously affiliated with a "long-term acute care" hospital recover when they return to the same or lower level of care.

Readmission from "home" may occur and if this occurs within 14 days of the first discharge to "home", then the primary endpoint will not be reached until such time as the participant has been at home for 14 consecutive days. Participants residing in a facility solely for public health or quarantine purposes will be considered as residing in the lowest level of required residence had these public health measures not been instated.

Supplemental statistical methods:

Unadjusted and adjusted proportional odds models (adjusted for the same covariates as in the Fine-Gray and Cox proportional hazards models) were used to analyze the association between plasma sRAGE and the 5-day ordinal pulmonary outcome. The proportional odds models were parameterized so that a summary odds ratio (OR) greater than 1 corresponded to better outcomes in the given group. Proportional odds models were fit using the "MASS" package in R version 3.6.0.

Supplemental Results:

Predictors of Day 5 Ordinal Outcome

We tested the association between baseline sRAGE concentration and the 5-day ordinal pulmonary outcome. Based on the model using $\log_2$-transformed continuous sRAGE as a predictor, each doubling in plasma sRAGE was associated with an unadjusted OR of 0.49 (95% CI 0.41-0.59) and a fully adjusted OR of 0.64 (95% CI 0.56-0.87) for favorable pulmonary outcome. However, the association between 5-day pulmonary outcome and baseline sRAGE quartile did not follow a linear pattern, with only the highest quartile of sRAGE demonstrating a significant association with 5-day pulmonary outcome when compared with the lowest quartile. Therefore, we next tested the association between a baseline sRAGE ≥ 6800 pg/mL and the 5day pulmonary ordinal outcome **(Supplemental 3)**. A baseline sRAGE concentration of 6800 pg/mL or higher was associated with an unadjusted OR for favorable pulmonary outcome of 0.10 (95% CI 0.06-0.18) as compared with the lowest three quartiles. The odds of favorable pulmonary outcome remained significantly lower among participants with plasma

sRAGE ≥ 6800 pg/mL after adjustment for baseline clinical and demographic characteristics, baseline supplemental oxygen requirement, viral antigen and antibody status, corticosteroid treatment, and plasma IL-6 concentration (OR 0.22, 95% CI 0.11-0.43). Five-day ordinal pulmonary outcomes by quartile of sRAGE for the combined treatment groups are shown in **Supplemental Figure 2**.

Because there was a significant interaction between baseline pulmonary status and dichotomous baseline sRAGE concentration in an unadjusted model for 5-day ordinal pulmonary outcome ($p<0.001$), we estimated the association between having plasma sRAGE concentration in the highest quartile and the 5-day pulmonary outcome within the following subgroups: participants requiring no supplemental oxygen (n = 76), those requiring supplemental oxygen but not HFNC/non-invasive ventilation (n = 160), and those requiring HFNC/non-invasive ventilation (n = 41). Only 5 participants with no baseline oxygen requirement had a plasma sRAGE above 6800 pg/mL, and there was no significant association between plasma sRAGE ≥6800 pg/mL and 5-day pulmonary outcome among these participants (OR 0.35, 95% CI 0.05-2.52). Among those requiring simple nasal cannula oxygen at any level, the summary odds ratio for more favorable pulmonary outcome at 5 days was 0.23 (95% CI 0.12 – 0.45) for participants with plasma sRAGE ≥6800 pg/mL compared to <6800 pg/mL. Among participants requiring HFNC or non-invasive ventilation, those with a plasma sRAGE level ≥6800 pg/mL had odds of a more favorable outcome 0.04 times those with lower plasma sRAGE levels (95% CI 0.01-0.19).

Supplemental Table 1. Spearman rank correlations between baseline biomarkers

	Protein C (% normal)	PAI-1 (ng/mL)	sRAGE (pg/mL)	IL-6 (pg/mL)	Ddimer	CRP (ug/mL)	Antigen (pg/mL)
Protein C (% Norm)	1	0.05	-0.14	-0.26	-0.21	-0.17	-0.15
PAI-1 (ng/mL)	0.05	1	0.24	0.11	-0.02	0.12	0.06
RAGE (pg/mL)	-0.14	0.24	1	0.41	0.1	0.31	**0.57**
IL-6 (pg/mL)	-0.26	0.11	0.41	1	0.34	0.35	0.36
D-dimer (ng/mL)	-0.21	-0.02	0.1	0.34	1	0.35	-0.04
CRP (ug/mL)	-0.17	0.12	0.31	0.35	0.35	1	0.2
Antigen (pg/mL)	-0.15	0.06	0.57	0.36	-0.04	0.2	1

Supplemental Table 2. Baseline plasma biomarker concentrations by baseline supplemental oxygen requirement

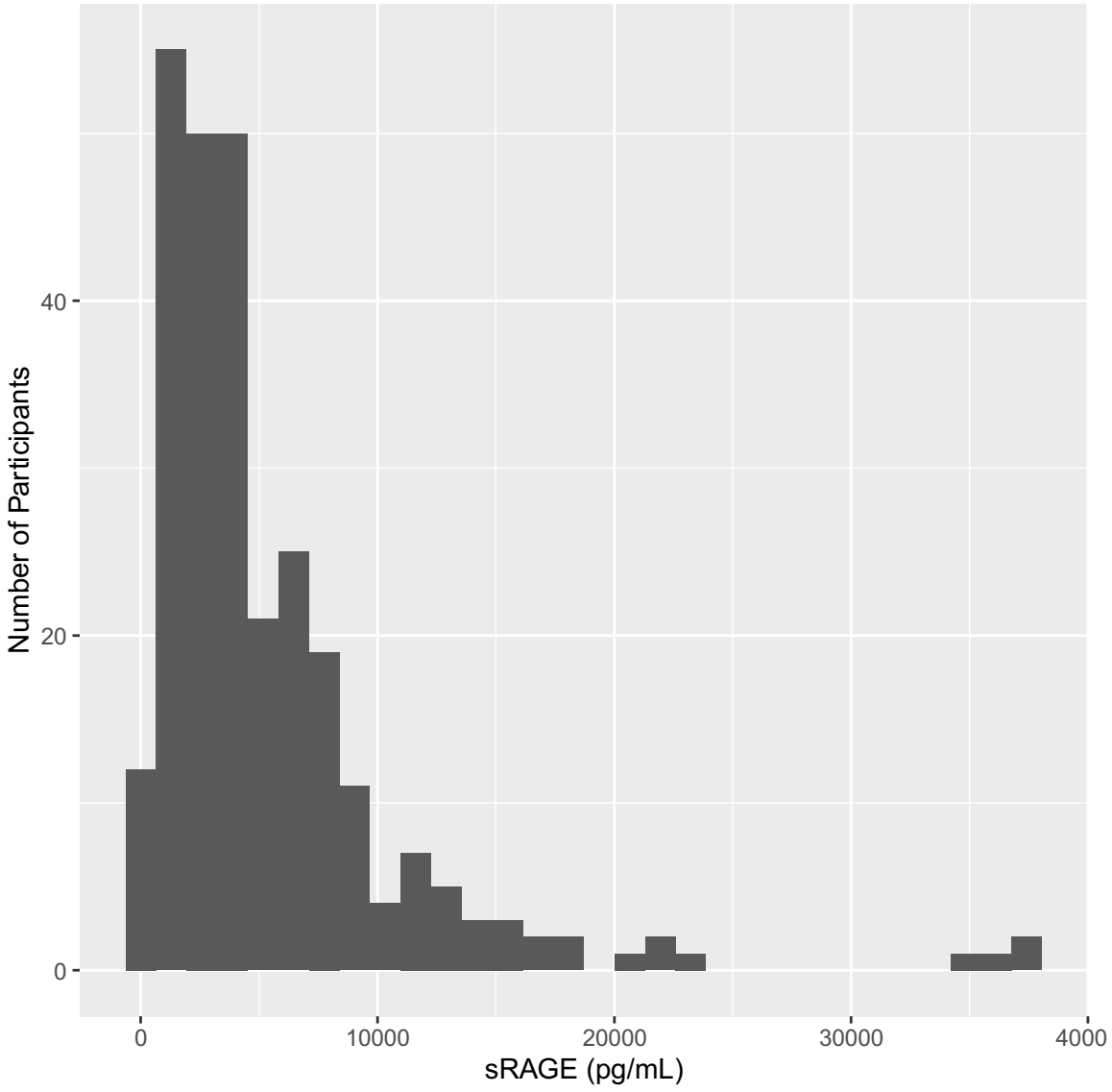
	No oxygen	Low oxygen (≤4 liters)	High oxygen (>4 liters)	High flow or non-invasive ventilation	p
sRAGE category (%)					<0.001
< 2000 pg/mL	29 (38.2)	22 (21.2)	11 (19.6)	7 (17.1)	
2000-3699 pg/mL	25 (32.9)	27 (26.0)	14 (25.0)	3 (7.3)	
3700-6799 pg/mL	17 (22.4)	33 (31.7)	11 (19.6)	8 (19.5)	
≥ 6800 pg/mL	5 (6.6)	22 (21.2)	20 (35.7)	23 (56.1)	
Positive anti-nucleocapsid antibody interpretation (%)	30 (39.5)	68 (65.4)	40 (71.4)	26 (63.4)	0.001
Viral antigen (pg/mL) (median [IQR])	800 [102, 1980]	1188 [203, 4290]	860 [98, 3110]	1861 [181, 4940]	0.084
IL-6 (pg/mL) (median [IQR])	8 [3, 15]	5 [2, 11]	6 [3, 18]	8 [3, 19]	0.27
D-dimer (ng/mL) (median [IQR])	822 [570, 1418]	831 [609, 1211]	1001 [800, 1288]	1273 [719, 2204]	0.005
CRP (ug/mL) (median [IQR])	27.83 [14, 56]	44 [26, 77]	56 [39, 95]	67 [36, 90]	<0.001
PAI-1 (ng/mL) (median [IQR])	4 [2, 5]	4 [3, 6]	3 [2, 6]	4 [3, 6]	0.39
Protein C (% normal) (median [IQR])	85 [62, 107.35]	90 [70, 111]	84 [62, 110]	84 [58, 112]	0.45

Supplemental Table 3. Association between plasma sRAGE and 5-day ordinal pulmonary outcome

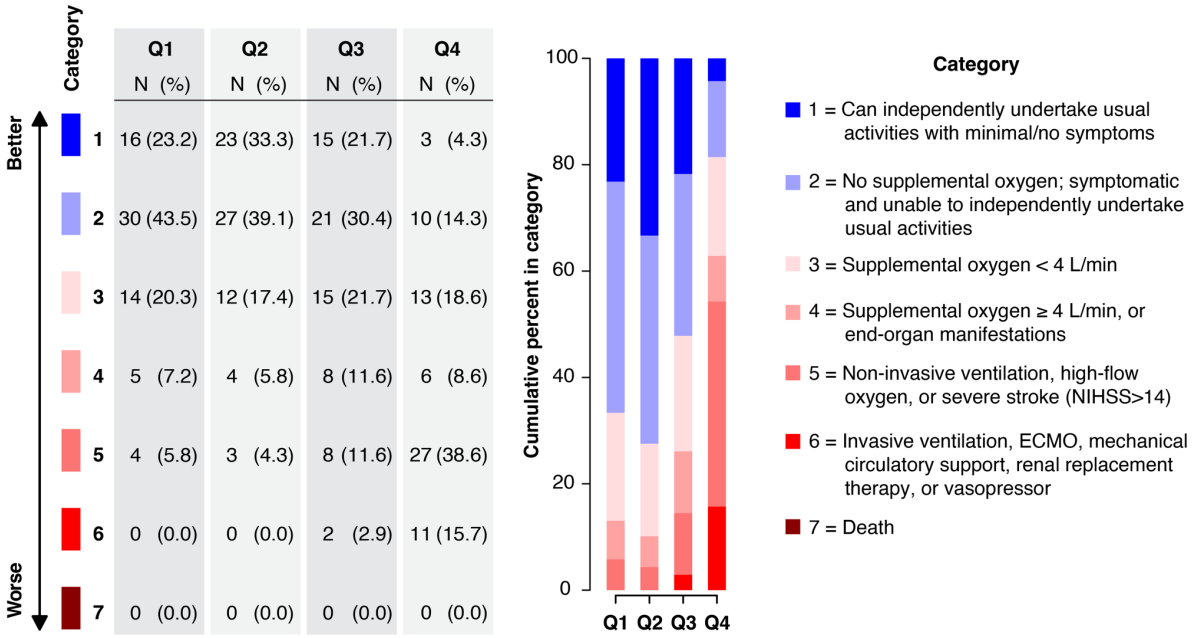
Per Quartile (unadjusted)			
	sRAGE (pg/mL)	**OR [95% CI]**	**p-value**
	< 2000	1.00 [1.00, 1.00]	-----
	2000-3699	1.43 [0.79, 2.60]	0.244
	3700-6799	0.62 [0.34, 1.13]	0.117
	≥6800	0.10 [0.05, 0.18]	< 0.001
Highest Quartile (6800 pg/mL) vs. Lower 3 Quartiles			
	sRAGE (pg/mL)	**Summary OR [95% CI]**	
Unadjusted	< 6800	1.00 [1.00, 1.00]	-----
	6800	0.10 [0.06, 0.18]	< 0.001
Adjusted for baseline oxygen requirement	< 6800	1.00 [1.00, 1.00]	-----
	≥6800	0.18 [0.10, 0.32]	< 0.001
Fully adjusted	< 6800	1.00 [1.00, 1.00]	-----
	≥ 6800	0.22 [0.11, 0.43]	< 0.001
Continuous (unadjusted)			
log_2(RAGE)		0.49 [0.41, 0.59]	<0.001

Fully adjusted model includes baseline supplemental oxygen requirement, log_2-transformed antigen level, endogenous antibody response (positive total anti-nucleocapsid), gender, age, body mass index, diabetes mellitus, presence of renal impairment, trial treatment allocation, corticosteroid treatment, and interleukin-6.

Supplemental Figures



Supplemental Figure 1. Distribution of plasma sRAGE in 277 participants.



Supplemental Figure 2. Pulmonary ordinal outcome at day 5 by plasma sRAGE quartile.