# Importance of Lung Epithelial Injury in COVID-19 Associated Acute Respiratory Distress Syndrome: Value of Plasma sRAGE

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# Importance of Lung Epithelial Injury in COVID-19 Associated Acute Respiratory Distress Syndrome: Value of Plasma sRAGE

Natacha Kapandji[1], MD; Elise Yvin[1,2], MD; Magali Devriese[2,3], MD; Constance de Margerie-Mellon[2,4], MD,PhD; Giulia Moratelli[1], MD ; Virginie Lemiale[1], MD ; Matthieu Jabaudon[5], MD, PhD ; Elie Azoulay[1,2], MD, PhD, Jean-Michel Constantin[6], MD, PhD; Guillaume Dumas[1,2] MD, PhD.

**Authors' affiliations:**

1- Medical Intensive Care Unit, Hôpital Saint-Louis, APHP, Paris, France

2- Université de Paris

3- Laboratoire d'immunologie et histocompatibilité, Hôpital Saint-Louis, APHP, Paris, France

4- Radiology department, Hôpital Saint-Louis, APHP, Paris, France

5- Department of Perioperative Medicine, CHU Clermont-Ferrand, Clermont-Ferrand, France, GReD, CNRS, INSERM, Université Clermont Auvergne, Clermont-Ferrand, France

6- Sorbonne University, GRC 29, AP-HP, DMU DREAM, Department of Anesthesiology and critical care, Pitié-Salpêtrière Hospital, Paris, France

**Running title:** Pulmonary edema in Sars-Cov2 infection

**Word numbering:** 998 words

**Keywords**: COVID-19; Acute respiratory distress syndrome; lung epithelial injury; Receptor for Advanced Glycation End-products.

**Sources of funding:** Université de Paris

**Authors Contributions**

GD, JMC, EY, NK designed and performed research; GD, JMC analyzed the data; GD, NK,

AJRCCM Articles in Press. Published May 25, 2021 as 10.1164/rccm.202104-1070LE

JMC wrote the manuscript; GD, JMC, EY, NK, GM, MD, CdM, MJ, EA collected the data; all authors approved the final manuscript.

**Corresponding Author:**

Guillaume Dumas, MD, PhD

Medical Intensive Care Unit, Saint-Louis teaching Hospital,

ECSTRRA team, Epidemiology and Clinical Statistics for Tumor, Respiratory, and Resuscitation Assessments, UMR 1153 (center of research in epidemiology and biostatistics, CRESS), INSERM, Université de Paris

Mailing address: Medical Intensive Care Unit, Hôpital Saint-Louis, 1 avenue Claude Vellefaux, 75010 Paris France

e-mail: dumas.guillaume1@gmail.com



AJRCCM Articles in Press. Published May 25, 2021 as 10.1164/rccm.202104-1070LE

*To the Editor,*

The respiratory form of the coronavirus disease (COVID-19) has led to an unprecedented number of hospitalizations for acute respiratory distress syndrome (ARDS). To date, pathophysiology of COVID-19 associated ARDS (CARDS) remains poorly understood. This has led to discuss a different presentation from non-COVID-19 ARDS, regarding lung mechanics abnormalities and hypoxemia mechanisms(1, 2).

However little attention has been paid to the value of biomarkers of lung injury. The soluble form of the receptor for advanced glycation end-products (sRAGE) is a well-characterized marker of lung alveolar epithelial injury(3) and has been associated with both prognostic and pathogenic values in patients with ARDS(4).

This study aims to investigate the value of baseline plasma sRAGE in CARDS and how it could differ between COVID-19 and non-COVID-19 ARDS.

**Patients and methods**

We prospectively enrolled all consecutive adult patients admitted to the medical intensive care unit of the Saint-Louis hospital, Paris, France between March 1st and June 1st, 2020 for CARDS according to the Berlin definition(5). This study was approved by the Ethics Committee of the *Société de Réanimation de Langue Française* (SRLF; **CE SRLF n°20-32**).

Management of patients included protective volume-controlled ventilation, neuromuscular blockers and prone position if needed. All measurements were performed within 24 hours post intubation. Ventilator's settings and respiratory mechanics measures were collected, together with dead space fraction, ventilatory ratio and, shunt fraction. When available, measurements of the Recruitment-to-Inflation (R/I) ratio measurement were collected(6). A Value up or equal to 0.5 was considered as a potential for lung recruitment.

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The severity of lung edema was assessed using the RALE score, evaluated by two independent physicians on the chest radiography of the day of MV initiation.

Levels of plasma sRAGE were measured in duplicate from thawed samples collected within 24 hours post MV initiation. A commercially available sandwich enzyme immunoassay kit (Human sRAGE Quantikine ELISA Kit, R&D Systems, Minneapolis, MN) was used following recommendations from the manufacturer.

Patients with CARDS were then compared to an historical multicentric prospective cohort of patients with ARDS in whom plasma sRAGE had been measured(7) and to control patients (eg. mechanically ventilated patients without COVID-19 infection nor ARDS, n=15).

Continuous variables are described as medians (interquartile ranges) and compared using the Wilcoxon's rank sum test or the Kruskal–Wallis test; categorical variables are summarized by counts (percent's) and compared using the exact Fisher test. Correlations were assessed with the Rho Spearman's correlation test. Prognosis value of sRAGE on day-90 mortality was assessed using Cox-model adjusted on potential confounders (e.g ARDS etiology, cardiovascular risk factors, BMI, driving pressure, PaO2/FiO2).

All tests were two-sided and p-values lower than 5% were considered to indicate significant associations. Analyses were performed using R statistical platform, version 3.0.2.

**Results**

*Characteristics of patients with COVID-19 ARDS* (***Table 1)***

Overall, 50 patients with CARDS (age 62.0 [54.0-68.7] years, 68% male) were included**.** Median time from symptoms onset to invasive MV initiation was 9.0 [7.0-14.0] days.

*Baseline plasma sRAGE correlates with lung injury severity and outcome in COVID-19*

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At baseline, plasma sRAGE was 4044.0 [1763.0-4768.0] pg/ml and significantly differed from control (525.0 pg/ml [411.0-638.5], p <0.001, **Figure 1**).

Baseline plasma sRAGE correlated with PaO2/FiO2 (Spearman's ρ = -0.49; p = 0.001), ventilatory ratio (ρ = 0.36; p = 0.019), shunt (ρ = 0.39; p = 0.01) and RALE score (median score 28 [18-36], ρ= 0.64; p<0.01).

The R/I ratio was measured in 16 patients (32%) and high potential for recruitability was observed in six (37.5%). Plasma sRAGE levels were higher in patients with high potential for recruitability (4245.0 pg/ml [3795.0-4854.0] vs 2890.0 pg/ml [2312.0-3566.0], p=0.02).

Of note, baseline plasma sRAGE was significantly higher in day-90 decedents than in survivors (4403.1 pg/ml [2564.0-4990.2] vs 2708.0 pg/ml [1965.9-4304.5], p = 0.04).

*Comparison between patients with CARDS and those with non-COVID-19 ARDS*

Compared with non-COVID-19 ARDS, patients with CARDS were significantly different with regards to BMI, cardiovascular risk factors and incidence of ARDS severity at day 1 (**Table 1**). Median static Crs was similar between ARDS patients with or without COVID-19 (29.5 [26.2-35.0] vs 28.6 [21.9-34.5] ml/cmH2O, respectively, p = 0.17).

Baseline sRAGE levels were significantly higher in CARDS compared to non-COVID-19 ARDS (4044.0 pg/ml [1763.0-4768.0] vs 2230.0 pg/ml [1156.0-3954.0], p = 0.005; **Figure 1**). Overall, day-90 mortality rate was 54% in CARDS and 36% in non-COVID-19 ARDS (p=0.045). Adjusted on potential confounders, baseline plasma sRAGE levels was significantly associated with mortality (adjusted HR: 1.51 [1.05 - 2.16] per one log increment, p=0.02).

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**Discussion**

Whether CARDS-related lung injury is alike other causes of ARDS is an important question. The answer may guide the ventilatory strategy and carry some prognostic information. Using a well-characterized marker of lung epithelial injury, this study suggests that CARDS includes a component of pulmonary alveolar damage higher than other causes of ARDS. Moreover, as in non COVID-19 ARDS, plasma sRAGE is associated with CARDS severity and outcome, especially lung edema, assessed by baseline RALE score and oxygenation impairment.

Since the pandemic onset, CARDS has been suggested to be an atypical subset of ARDS (2, 8). This assertion has been recently challenged, mainly through comparisons of lung mechanics parameters(9). Although sRAGE production could have several sources, numerous works have provided evidence that alveolar type I cells are the main source of plasma sRAGE, and that sRAGE is a reliable marker of diffuse lung alveolar injury and impaired fluid clearance in both clinical and experimental models of ARDS(3). In this study, we found a marked elevation in sRAGE levels among patients with CARDS, which argues for intense lung epithelial injury. This is consistent with recent pathological reports from post-mortem lung biopsies, where diffuse alveolar damage was the most common histological finding(10).

This study has some limitations. First, the limited number of patients from a single center requires additional data to confirm this hypothesis. Second, plasma sRAGE was only measured at baseline and the value of changes over time is unknown.

In summary, our findings suggest that lung epithelial injury, as reflected by plasma sRAGE, may be a key pathophysiological feature with prognostic information in CARDS.

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**Table 1.** Comparisons between patients with SARS-CoV2 related ARDS and patients with non-ARDS from others causes

| | **COVID-19 ARDS N=50** | **Non-COVID-19 ARDS N=117** | **p-value** |
|---|---|---|---|
| *Demographic* | | | |
| Age, years | 62.0 [54.0-68.7] | 60.0 [45.0-70.0] | 0.38 |
| Male gender | 34 (68) | 80 (68) | 1.00 |
| BMI, kg/m2 | 27.7 [24.3-30.7] | 25.9 [22.2-28.5] | 0.008 |
| Hypertension | 27 (54) | 38 (32) | 0.015 |
| Diabetes | 18 (36) | 22 (19) | 0.029 |
| Dyslipidemia | 24 (48) | 17 (15) | <0.0001 |
| At least one cardiovascular risk factor | 32 (64) | 54 (46) | 0.052 |
| SAPS II | 45.0 [36.0-56.0] | 49.0 [39.0-64.0] | 0.10 |
| *ARDS cause* | | | <0.05 |
| Pulmonary | 50 (100) | 85 (73) | |
| Lung infection | 50 (100) | 85 (100) | |
| Extra-pulmonary | - | 27 (27) | |
| Intraabdominal infection | - | 22 (81) | |
| Acute pancreatitis | - | 5 (19) | |
| *ARDS severity* | | | 0.001 |
| Mild | 13 (26) | 8 (7) | |
| Moderate | 24 (48) | 56 (48) | |
| Severe | 13 (26) | 52 (45) | |
| *Respiratory parameters, day 1* | | | |
| $V_T$, ml/kg PBW | 6.0 [6.0-6.17] | 6.6 [6.0-7.3] | <0.0001 |
| Pplat, cmH2O | 23.0 [21.0-25.0] | 28.0 [24.0-30.0] | <0.0001 |
| PEEP, cmH2O | 10.0 [8.0-12.0] | 10.0 [8.0-13.0] | 0.57 |
| Crs, ml/cm2O | 29.5 [26.2-35.0] | 28.6 [21.9-34.5] | 0.17 |

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| | | | |
|---|---|---|---|
| Ventilatory ratio | 1.6 [1.4-1.9] | 2.0 [1.7-2.4] | <0.0001 |
| *Biological data* | | | |
| PaO2/FiO2, mmHg | 126 [99.25-199.8] | 107.2 [71.11-147.2] | 0.005 |
| pH | 7.38 [7.34-7.42] | 7.35 [7.27-7.40] | 0.008 |
| paCO2, mmHg | 40.5 [36.9-45.8] | 44.0 [37.7-50.0] | 0.070 |
| Baseline plasma sRAGE, pg/ml | 4044.0 [1763.0-4768.0] | 2230.0 [1156.0-3954.0] | 0.005 |
| *Treatments* | | | |
| Prone position use | 28 (56) | 24 (21) | <0.0001 |
| NO therapy | 4 (8) | 33 (28) | 0.007 |
| VV-ECMO | 4 (8) | 2 (2) | 0.11 |
| *Outcomes* | | | |
| Duration of MV, days | 12.0 [4.0-17.0] | 11.0 [6.0-20.0] | 0.31 |
| ICU LOS, days | 14.0 [10.0-22.0] | 18.0 [10.0-34.2] | 0.063 |
| In ICU mortality | 27 (54) | 38 (33) | 0.016 |
| Day-90 mortality | 27 (54) | 42 (36) | 0.045 |

Results are presented as N(%) or median [IQR]

ARDS: Acute respiratory distress syndrome; SAPSII: simplified acute physiology score; $V_T$: Tidal volume; PBW: predicted body weight; Pplat: inspiratory plateau pressure; PEEP: positive end expiratory pressure; Crs: static compliance of respiratory system ; PaO2: partial pressure of oxygen; FiO2: fraction of inspired oxygen, PaCO2: partial pressure of carbon dioxide; sRAGE: Soluble receptor for advanced glycation end-products; NO: nitric oxide therapy; VV-ECMO: veno-venous extra-corporal membrane oxygenation; ICU: Intensive Care Unit ; LOS: length of stay

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**Figure legend**

**Figure 1. Value of plasma soluble receptor for advanced glycation end-products (sRAGE) levels at baseline in patients with COVID-19 or non-COVID-19 ARDS.**

(A) Comparison of sRAGE levels between survivors and non survivors in patients with COVID-19 ARDS. (B) Correlations between baseline plasma sRAGE and RALE score in patients with COVID-19 ARDS. (C) Plasma sRAGE levels in a subset of 16 patients with measurement of Recruitment/Inflation (R/I) ratio available on the day of mechanical ventilation initiation. (D) Comparison of plasma sRAGE levels in patients with COVID-19, patients with non-COVID-19 ARDS, and control patients.

Correlations have been tested with the calculation of Spearman's rank correlation coefficient R (rho). ARDS: acute respiratory distress syndrome.

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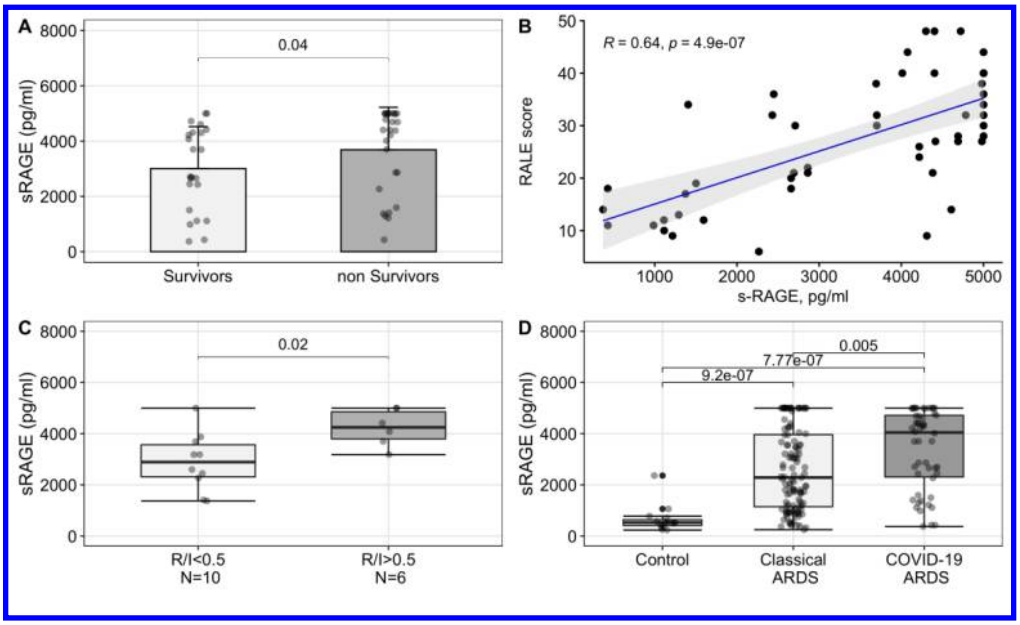


Figure 1. Value of plasma soluble receptor for advanced glycation end-products (sRAGE) levels at baseline in patients with COVID-19 or non-COVID-19 ARDS.

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