BRIEF REPORT

OPEN

Soluble Suppression of Tumorigenicity-2 Associates With Ventilator Dependence in Coronavirus Disease 2019 Respiratory Failure

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OBJECTIVES: We hypothesize that elevated soluble suppression of tumorigenicity-2 concentrations, a marker of pulmonary epithelial injury, reflect ongoing lung injury in acute hypoxemic respiratory failure due to coronavirus disease 2019 and associate with continued ventilator dependence.

DESIGN: We associated serial plasma soluble suppression of tumorigenicity-2 levels and markers of systemic inflammation including D-dimer, C-reactive protein, and erythrocyte sedimentation rate with 30-day mortality and ventilator dependence.

SETTING: Adult medical ICUs and general medicine wards at an academic teaching hospital in Boston, MA.

PATIENTS: Adult patients with severe acute respiratory syndrome coronavirus 2 infection and acute hypoxemic respiratory failure admitted to the ICU ($n = 72$) and non-ICU patients managed with supplemental oxygen ($n = 77$).

INTERVENTIONS: Observational study from April 25 to June 25, 2020.

MEASUREMENTS AND MAIN RESULTS: ICU patients had a higher baseline body mass index and median soluble suppression of tumorigenicity-2, D-dimer, and C-reactive protein concentrations compared with non-ICU patients. Among ICU patients, elevated baseline modified Sequential Organ Failure Assessment score and log (soluble suppression of tumorigenicity-2) were associated with 30-day mortality, whereas initial Pao_2/Fio_2 and markers of systemic inflammation were similar between groups. Only log (soluble suppression of tumorigenicity-2) associated with ventilator dependence over time, with the last measured log (soluble suppression of tumorigenicity-2) concentration obtained on ICU day 11.5 (interquartile range [7–17]) higher in patients who required reintubation or tracheostomy placement compared with patients who were successfully extubated (2.10 [1.89–2.26] vs 1.87 ng/mL [1.72–2.13 ng/mL]; $p = 0.03$). Last measured systemic inflammatory markers, modified Sequential Organ Failure Assessment score, and Pao_2/Fio_2 were not different between patients who were successfully extubated compared with those with continued ventilator dependence.

CONCLUSIONS: Plasma soluble suppression of tumorigenicity-2 is a biomarker readily measured in blood that can provide dynamic information about the degree of a patient's lung injury and real-time assessment of the likelihood of extubation success. Measures of systemic inflammation, illness severity, and oxygenation did not associate with ventilator outcomes.

KEY WORDS: acute respiratory distress syndrome; biomarkers; coronavirus disease 2019 virus disease; ventilator weaning

The management of coronavirus disease 2019 acute hypoxemic respiratory failure (CoV19-AHRF) remains a significant challenge, often characterized by prolonged mechanical ventilation and ICU admission (1). Although elevated inflammatory markers correlate with disease progression

and mortality, there is a critical need for specific measures of ongoing lung injury and predictors of ventilator dependence to guide treatment and prognostication in CoV19-AHRF (2–4). Soluble suppression of tumorigenicity-2 (sST2) is a member of the interleukin (IL)–1 receptor family and is the soluble isoform of the IL-33 receptor. It likely serves as a circulating decoy receptor in several inflammatory disorders and is a marker of pulmonary epithelial injury (5). We previously reported an association of circulating sST2 with ventilator dependence, reintubation, and mortality in acute hypoxemic respiratory failure (AHRF) (6, 7). Based on these findings, we hypothesized that elevated sST2 concentrations reflect ongoing lung injury in CoV19-AHRF and associate with ventilator dependence.

MATERIALS AND METHODS

We studied adult ICU patients with severe acute respiratory syndrome coronavirus 2 infection and AHRF and non-ICU patients with mild hypoxemia managed with 2–6 L/min supplemental oxygen who were consecutively admitted to Massachusetts General Hospital between April 25 and June 25, 2020. Patients were excluded if they were transferred from an outside hospital or had life-sustaining treatment withdrawn within the first 6 days of admission. Baseline laboratory values were defined as first available, within 72 hours of admission. Successful extubation was defined as extubation without reintubation or tracheostomy placement. The study was approved by the Massachusetts General Hospital institutional review board (protocol number 2015P001650). Informed consent was waived.

Plasma samples ($n = 579$) were collected from excess clinical blood draws daily for the first 6 days after admission and on the day of extubation in intubated patients, when available. Samples were stored in EDTA-treated plasma at –80°C and quantified using a highly sensitive sST2 assay (Critical Diagnostics, San Diego, CA).

Summary statistics of patient demographics, laboratory values, clinical characteristics, and 30-day outcomes were collected. The Shapiro-Wilk test was used to assess for normal distribution. Differences between groups were compared using Fisher exact test for categorical variables and the Student t test or Mann-Whitney nonparametric test for continuous variables, as appropriate. Nonparametric data were logarithmically transformed for further analyses. We created a multivariable logistic regression model for successful extubation using log-sST2 and baseline covariates and obtained adjusted odds ratios (ORs) and 95% CIs. Receiver operating characteristic (ROC) curve analysis was performed for sST2 values and 30-day ventilator outcomes. Analyses were performed in GraphPad Prism Version 9.0 (GraphPad Software, San Diego, CA). A two-sided p value of less than or equal to 0.05 was considered statistically significant.

RESULTS

ICU patients ($n = 72$) had a mean age of 60 years with a modified Sequential Organ Failure Assessment (mSOFA) score of 7 and Pao_2/Fio_2 of 150 on ICU admission (**Supplement Digital Content 1**, http://links.lww.com/CCX/A701). Non-ICU patients ($n = 77$) had a mean age of 61 years with a coronavirus disease 2019 (COVID-19) ordinal scale score of 4 and supplemental oxygen requirement of 3 L/min on hospital admission. ICU patients had a higher mean body mass index (31.6 ± sd 7.7 vs 29.0 ± 6.0; $p = 0.02$) and higher baseline median sST2 (85, interquartile range [68–161] vs 46 [34–67]; $p < 0.0001$), d-dimer (1,684 [1,088–2,888] vs 1,040 [737–1,810]; $p = 0.007$, and C-reactive protein (CRP) (134 [62–194] vs 72 [42–150]; $p = 0.04$) concentrations compared with non-ICU patients, whereas ferritin (988 [419–1,828] vs 695 [363–1,326]; $p = 0.20$) and erythrocyte sedimentation rate (56 [34–90] vs 45 [38–75]; $p = 0.83$) concentrations were similar between groups.

Of the ICU patients, 42 patients (58%) were successfully extubated and 30 patients (42%) were reintubated, had a tracheostomy placed, or died by day 30 (**Supplemental Digital Content 2**, http://links.lww.com/CCX/A701). Biomarker values were logarithmically transformed to analyze their association with 30-day outcomes. Baseline log-sST2 concentrations were elevated in ICU nonsurvivors compared with survivors (2.08 [1.87–2.52] vs 1.94 ng/mL [1.83–2.07 ng/mL]; $p = 0.05$) (**Fig. 1**). Baseline log-transformed concentrations of ferritin (2.90 [2.49–2.90] vs 3.02 [2.66–3.34]; $p = 0.31$), d-dimer (3.26 [3.09–3.91] vs 3.19 [2.97–3.45]; $p = 0.21$), and CRP (2.17 [1.86–2.31] vs 2.13 [1.79–2.29]; $p = 0.53$) were not different between groups. Baseline mSOFA score was higher in ICU nonsurvivors (8 [7.25–9] vs 7 [5–8]; $p = 0.009$), but initial Pao_2/Fio_2 was similar between groups (133 [88–167] vs 136 [99–195]; $p = 0.35$).
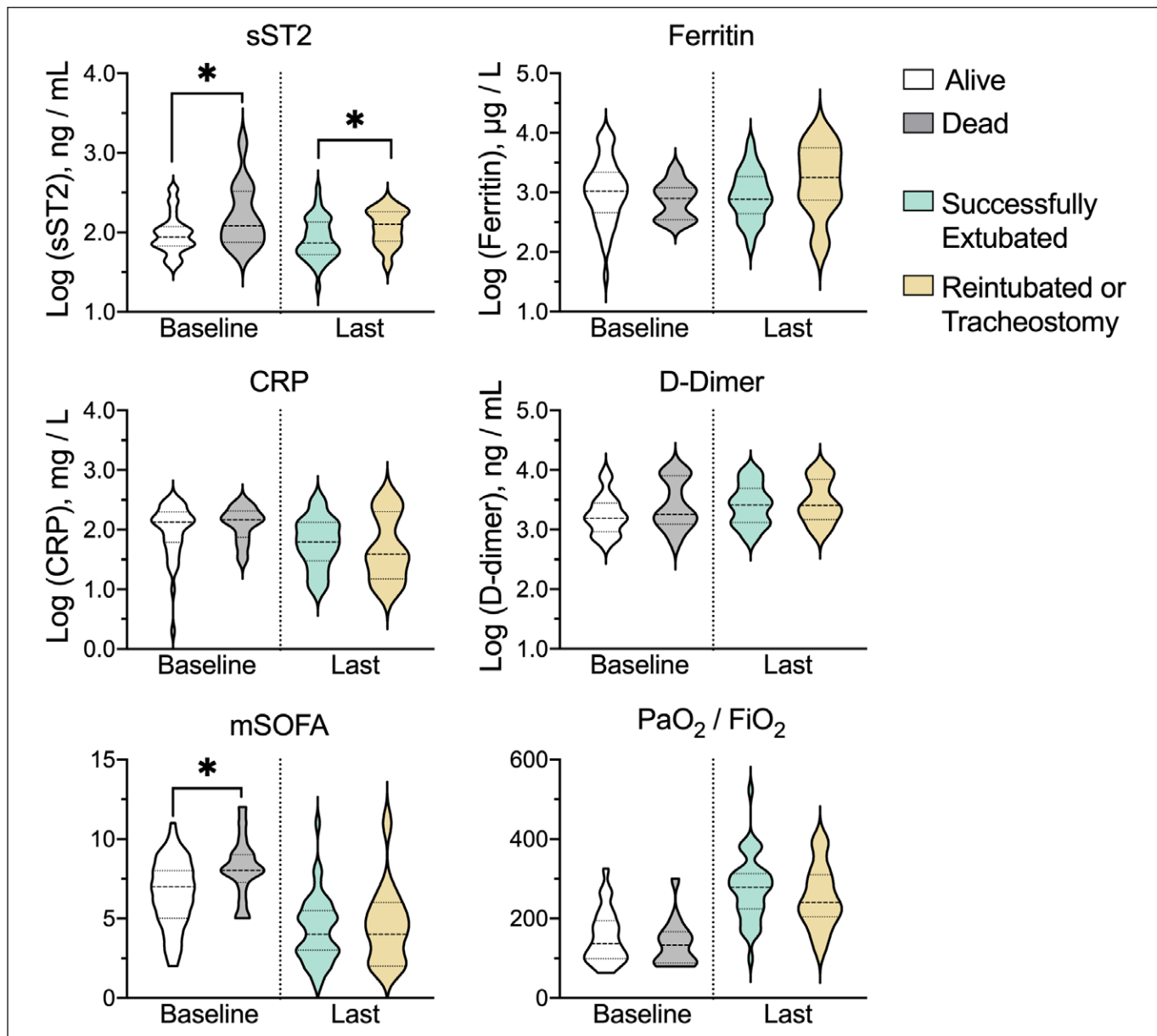
Figure 1. Elevated plasma soluble suppression of tumorigenicity-2 (sST2) levels associate with 30 d mortality and ventilator dependence in coronavirus disease 2019 (COVID-19) acute hypoxemic respiratory failure (AHRF). Elevated baseline sST2 concentration and modified Sequential Organ Failure Assessment (mSOFA) score associate with 30 d ICU mortality. Elevated last measured sST2 concentration (measured on median day 11.5 [7–17]) associates with need for reintubation or tracheostomy in COVID-19 AHRF, whereas concurrently measured systemic inflammatory markers, mSOFA score, and Pao_2/Fio_2 remain similar in patients successfully extubated compared with those with persistent ventilator dependence. Biomarker values logarithmically transformed for analysis. Data presented as violin plots displaying scaled distribution of data for each group with medians and quartiles. $p < 0.05$. CRP = C-reactive protein.

As age and mSOFA score were different between patients who were successfully extubated and patients who required reintubation, tracheostomy placement, or died at day 30 (Supplemental Digital Content 2, http://links.lww.com/CCX/A701), we created a multivariable logistic regression model for the association between log-sST2 values and extubation success adjusting for these baseline covariates. Only log-sST2 was associated with successful extubation in this analysis, with an adjusted OR 0.10 (95% CI, 0.01–0.69; $p = 0.03$) for extubation success for every 1-log unit increase in sST2 concentration (**Supplemental Digital Content 3**, http://links.lww.com/CCX/A701).

sST2 concentrations remained elevated over the first 5 days of the ICU admission in patients who died or required tracheostomy or reintubation compared with patients successfully extubated (**Supplemental Digital Content 4**, http://links.lww.com/CCX/A701). The last measured sST2 concentration was obtained on median day 11.5 (7–17), which included the day of extubation in 44 patients. The last measured log-sST2 concentration was higher in patients who required reintubation or tracheostomy placement compared with patients who were successfully extubated (2.10 [1.89–2.26] vs 1.87 ng/mL[1.72–2.13 ng/mL]; p = 0.03) (Fig. 1) with an area under the ROC curve of 0.70 (95% CI, 0.54–0.85; p = 0.03) (**Supplemental Digital Content 5**, http://links.lww.com/CCX/A701). In contrast, the last measured systemic inflammatory markers (ferritin, CRP, and D-dimer) and clinical indices (mSOFA score and Pao_2/Fio_2) were similar in patients who were successfully extubated compared with those who required reintubation or tracheostomy placement (Fig. 1).

DISCUSSION

Plasma concentrations of sST2 associate with disease course and have discriminatory value for ventilator dependence in CoV19-AHRF. Recent studies demonstrate that sST2 values followed longitudinally are highly associated with illness severity and mortality in COVID-19 (4, 8). To our knowledge, this is the first study that associates a plasma biomarker with ventilator dependence in CoV19-AHRF. Our data suggest that, in patients with CoV19-AHRF, elevated sST2 concentrations over the course of an ICU admission may signify persistent lung injury and need for continued ventilatory support. Given the association between sST2 and epithelial lung injury and outcomes in AHRF, its measurement may provide critical insight into a patient's degree of underlying lung injury, likelihood of extubation success, and clinical trajectory beyond current routine assessments of illness severity and oxygenation (5).

This study has important limitations. This is a single-center, retrospective study that represents institutional practice at the time including early intubation and avoidance of noninvasive ventilation (NIV) due to concerns for disease transmission. This study was performed prior to the routine administration of steroids for CoV19-AHRF (9). However, in other disease states, inflammation mediated by sST2 and its ligand IL-33 is typically steroid resistant with steroids showing no meaningful effect on sST2 concentrations (10). The effects of increased application of NIV and steroid use on measures of lung injury remain important areas of investigation. Additionally, although we measured plasma and not bronchoalveolar lavage sST2 levels, circulating sST2 levels are known to correlate with bronchial aspirate values (5).

We conclude that plasma sST2 may provide a circulating measure of local lung injury in CoV19-AHRF and provide important prognostic information about a patient's clinical trajectory and readiness for ventilator liberation beyond standard physiologic assessment alone. Prospective trials using sST2 levels to guide ventilator management and targeted interventions in CoV19-AHRF are warranted.

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