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Evaluation of Albumin Kinetics in Critically Ill Patients With Coronavirus Disease 2019 Compared to Those With Sepsis-Induced Acute Respiratory Distress Syndrome

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OBJECTIVES: This report aims to characterize the kinetics of serum albumin in critically ill patients with coronavirus disease 2019 compared with critically ill patients with sepsis-induced acute respiratory distress syndrome.

DESIGN: Retrospective analysis.

SETTING: We analyzed two critically ill cohorts, one with coronavirus disease 2019 and another with sepsis-induced acute respiratory distress syndrome, treated in the New York Presbyterian Hospital-Weill Cornell Medical Center.

PATIENTS: Adult patients in the coronavirus disease 2019 cohort, diagnosed through reverse transcriptase-polymerase chain reaction assays performed on nasopharyngeal swabs, were admitted from March 3, 2020, to July 10, 2020. Adult patients in the sepsis-induced acute respiratory distress syndrome cohort, defined by Sepsis III criteria receipt of invasive mechanical ventilation and a Pao_2/Fio_2 ratio less than 300 were admitted from December 12, 2006, to February 26, 2019.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: We evaluated serial serum albumin levels within 30 days after ICU admission in each cohort. We then examined the albumin progression trajectories, aligned at ICU admission time to test the relationship at a similar point in disease progression, in survivors and nonsurvivors. Albumin trajectory in all critically ill coronavirus disease 2019 patients show two distinct phases: phase I (deterioration) showing rapid albumin loss and phase II (recovery) showing albumin stabilization or improvement. Meanwhile, albumin recovery predicted clinical improvement in critical coronavirus disease 2019. In addition, we found a deterioration and recovery trends in survivors in the sepsis-induced acute respiratory distress syndrome cohort but did not find such two-phase trend in nonsurvivors.

CONCLUSIONS: The changes in albumin associated with coronavirus disease 2019 associated respiratory failure are transient compared with sepsis-associated acute respiratory distress syndrome and highlight the potential for recovery following a protracted course of severe coronavirus disease 2019.

KEY WORDS: acute respiratory distress syndrome; albumin; coronavirus disease 2019; sepsis

Coronavirus disease 2019 (COVID-19) has been associated with alterations in many acute phase proteins such as albumin (1). Indeed, a lower albumin at admission to the hospital has been associated with a higher mortality in COVID-19 (2). However, it is unclear whether albumin changes in COVID-19 are more pronounced than other forms of critical illness associated with changes in vascular permeability (3). Our objective was to characterize the kinetics of serum albumin in critically ill patients with COVID-19 compared

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with critically ill patients with sepsis-induced acute respiratory distress syndrome (ARDS).

METHODS

We did a retrospective study at the New York Presbyterian Hospital-Weill Cornell Medical Center that compared two critically ill cohorts with COVID-19 (4) and sepsis-induced ARDS (5, 6), respectively. Adult patients in the COVID-19 cohort were admitted from March 3, 2020, to July 10, 2020. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnosis was made through reverse transcriptase-polymerase chain reaction assays performed on nasopharyngeal swabs. The critical care response to the pandemic has been previously described (7). All patients had a Pao_2/Fio_2 ratio less than 300. COVID-19 patients receiving invasive mechanical ventilation outside ICU settings were considered as critically ill and included in this study. In addition, adult patients with sepsis-induced ARDS, defined by Sepsis III criteria (8) receipt of invasive mechanical ventilation and a Pao_2/Fio_2 ratio less than 300 and who were admitted from February 15, 2011, to February 26, 2019, where included.

We evaluated serial serum albumin levels within 30 days after ICU admission in each cohort. We averaged albumin values over 24 hours if more than one value was available. We then examined the albumin progression trajectories, aligned at ICU admission time to test the relationship at a similar point in disease progression, in survivors and nonsurvivors (defined by 30-d mortality). We hypothesized that albumin recovery would be apparent in survivors in both cohorts. We derived an algorithm based on Chow test (9) to detect the albumin trajectory breakpoint for each patient, where a deteriorating albumin trend changed to a recovering trend. Specifically, for each patient, the Chow test was performed for each time point of the albumin trajectory, and the breakpoint was determined by rejection ($p < 0.05$ and F value ≥ 3) of the null hypothesis that the coefficients of linear regressions before and after the breakpoint are equal. After that, we fit linear mixed-effects models to estimate the deteriorating and recovering trajectories, for survivors and nonsurvivors, respectively, adjusting for age, sex, and comorbidities.

To assess impact of the use of albumin transfusion, we performed a sensitivity analysis. Specifically, patients who received an albumin transfusion within 10 days following ICU admission in the COVID-19 cohort were excluded. We then refitted the linear mixed-effects model in this subpopulation. Data on albumin transfusions were not available in the Sepsis-induced ARDS population.

We reported descriptive data as mean (SD) or median (interquartile range [IQR]) for continuous variables and number (percentage) for categorical variables. We assessed the differences between groups using Fisher exact test for categorical values, and two-sample *t* test or Wilcoxon rank-sum test for continuous values where appropriate. All the tests were two-sided with a significance level of 0.05.

The study was approved by the Institutional Review Board at Weill Cornell Medicine Number 20-04021909, Number 1811019761.

RESULTS

The COVID-19 cohort consists of 336 critically ill patients with confirmed SARS-CoV-2 infection (age, 62.5 yr [SD = 14.7 yr]; 31.0% female). One-hundred two COVID-19 patients died prior to extubation during their hospitalization and 234 were survivors. The nonsurvivors were older than the survivors (67.3 yr [SD = 12.1 yr] vs 60.4 yr [SD = 15.2 yr]; $p < 0.001$). There was no significant difference of comorbidities between the nonsurvivors and survivors. Baseline albumin level was lower in the nonsurvivors than that in the survivors (2.03 g/dL [SD = 0.50 g/dL] vs 2.19 g/dL [SD = 0.45 g/dL]; $p = 0.008$).

The sepsis-induced ARDS cohort contains 413 critically ill patients with confirmed sepsis (age, 69.3 yr [SD = 17.1 yr]; 40.2% female), of which 75 were nonsurvivors and 338 were survivors at 30 days. Overall, the patients with sepsis-induced ARDS showed a higher burden of chronic comorbidities than the COVID-19 patients. Compared with the sepsis-induced ARDS patients, the COVID-19 patients had a higher baseline Sequential Organ Failure Assessment score (for nonsurvivors: 13 [IQR, 11–15] vs 12 [IQR, 9–14; $p = 0.002$] and for survivors: 12 [IQR, 11–13] vs 8 [IQR, 6–11; $p < 0.001$]). More details of the characteristics of the two cohorts are shown in **Table 1**.

Albumin trajectory in all critically ill COVID-19 patients consists of two clearly distinct phases (**Fig. 1**). Phase I (deterioration) was defined by rapid albumin loss and phase II (recovery) showed albumin stabilization or improvement. The Chow test detected albumin breakpoint for each patient occurred 6.38 days (SD = 4.21 d) after admission versus 6.96 days

TABLE 1.
Clinical Characteristics of the Studied Coronavirus Disease 2019 and Sepsis Cohorts

	Coronavirus Disease 2019 Cohort				Sepsis Cohort			
Variable	**Total**	**Nonsurvivors**	**Survivors**	***p*[a]**	**Total**	**Nonsurvivors**	**Survivors**	***p*[a]**
Number of patients	336	102	234	–	413	75	338	–
Demographics								
Age, yr, mean (SD)	62.5 (14.7)	67.3 (12.1)	60.4 (15.2)	< 0.001	69.3 (17.1)	74.5 (16.7)	68.2 (17.0)	0.004
Sex, female, *n* (%)	104 (31.0)	27 (26.5)	77 (32.9)	0.251	166 (40.2)	29 (38.7)	137 (40.5)	0.795
Race, White, *n* (%)	110 (32.7)	33 (32.4)	77 (32.9)	1	133 (32.2)	25 (33.3)	108 (32.0)	0.891
Body mass index, kg/m^2, mean (SD)	29.3 (8.0)	28.6 (7.8)	29.5 (8.1)	0.231	29.2 (14.3)	26.6 (6.0)	29.8 (15.4)	0.043
Comorbidities, *n* (%)								
Active cancer (liquid)	14 (4.2)	7 (6.9)	7 (3.0)	0.135	36 (8.7)	13 (17.3)	23 (6.8)	0.006
Active cancer (solid)	9 (2.7)	4 (3.9)	5 (2.1)	0.462	36 (8.7)	4 (5.3)	32 (9.5)	0.364
Congestive heart failure	68 (20.2)	22 (21.6)	46 (19.7)	0.767	146 (35.4)	25 (33.3)	121 (35.8)	0.789
Hypertension	184 (54.8)	59 (57.8)	125 (53.4)	0.476	243 (58.8)	40 (53.3)	203 (60.1)	0.301
Pulmonary disease	69 (20.5)	23 (22.5)	46 (19.7)	0.559	120 (29.0)	22 (29.3)	98 (29.0)	1
Diabetes mellitus	100 (29.8)	33 (32.4)	67 (28.6)	0.517	107 (25.9)	16 (21.3)	91 (26.9)	0.382
Renal disease	29 (8.6)	10 (9.8)	19 (8.1)	0.673	101 (24.5)	18 (24.0)	83 (24.6)	1
Liver disease	6 (1.8)	4 (3.9)	2 (0.9)	0.071	70 (16.9)	22 (29.3)	48 (14.2)	0.003
Pao_2/Fio_2 ratio at baseline, mean (SD)	169.6 (92.8)	166.6 (106.6)[b]	170.9 (6.0)[c]	0.562	205.8 (197.1)	147.0 (93.7)[b]	216.0 (208.3)[c]	< 0.001
Sequential Organ Failure Assessment at baseline, median (interquartile range)	12 (11–14)	13 (11–15)[d]	12 (11–13)[e]	< 0.001	9 (7–11)	12 (9–14)[d]	8 (6–11)[e]	< 0.001
Albumin level at baseline, g/dL, mean (SD)	2.14 (0.47)	2.03 (0.50)	2.19 (0.45)	0.008	2.61 (0.71)	2.30 (0.79)	2.67 (0.68)	0.019

(*Continued*)

TABLE 1. (*Continued*).
Clinical Characteristics of the Studied Coronavirus Disease 2019 and Sepsis Cohorts

	Coronavirus Disease 2019 Cohort				Sepsis Cohort			
Variable	Total	Nonsurvivors	Survivors	*p*[a]	Total	Nonsurvivors	Survivors	*p*[a]
Breakpoint of albumin trajectories[f]								
Time of breakpoint, d (after intubation), mean (SD)	6.50 (4.13)	6.38 (4.21)	6.96 (3.81)	0.141	–	–	9.44 (5.03)	–
Albumin level at break point, g/dL, mean (SD)	1.57 (0.38)	1.44 (0.39)	1.61 (0.36)	0.003	–	–	2.14 (0.47)	–
Infection source, *n* (%)								
Pneumonia	–	–	–	–	173 (41.9)	42 (56.0)	131 (38.8)	0.007
Urinary tract	–	–	–	–	77 (18.6)	8 (10.7)	69 (20.4)	0.050
Intra-abdominal	–	–	–	–	75 (18.2)	19 (25.3)	56 (16.6)	0.096

[a]The *p* values were calculated to assess the differences between nonsurvivors and survivors, using Fisher exact test for categorical values, and two-sample *t* test or Wilcoxon rank-sum test for continuous values where appropriate.
[b]$p = 0.106$ for cross-cohort comparison of baseline Pao_2/Fio_2 (P/F) ratio of nonsurvivors.
[c]$p < 0.001$ for cross-cohort comparison of baseline P/F ratio of survivors.
[d]$p = 0.002$ for cross-cohort comparison of baseline Sequential Organ Failure Assessment (SOFA) score of nonsurvivors.
[e]$p < 0.001$ for cross-cohort comparison of baseline SOFA score of survivors.
[f]We identified significant break points of albumin trajectories for both survivors and nonsurvivors in the coronavirus disease 2019 cohort and for survivors in the sepsis-induced acute respiratory distress syndrome cohort, based on Chow test.
Dashes indicates no *p* value calculated.

(SD = 3.81 d) after admission ($p = 0.141$), in survivors and nonsurvivors, while the breakpoint albumin level was lower in nonsurvivors compared with that in survivors (1.44 g/dL [SD = 0.39 g/dL] vs 1.61 g/dL [SD = 0.36 g/dL]; $p = 0.003$) (Table 1 and Fig. 1*A*). Based on the breakpoint for each patient, linear mixed-effects models identified clear deterioration phases with similar slopes (i.e., rates of daily change of albumin level), among nonsurvivors (β = –0.081; 95% CI, –0.088 to –0.074; $p < 0.001$) and survivors (β = –0.074; 95% CI, –0.079 to –0.070; $p < 0.001$) (Fig. 1*A*). Following the deterioration phase, there was a recovery phase in survivors (β = 0.028; 95% CI, 0.027–0.030; $p < 0.001$), that was higher than nonsurvivors (β = –0.002; 95% CI, –0.005 to 0.002; $p = 0.393$). In the sepsis-induced ARDS cohort, we found a deterioration (β = –0.015; 95% CI, –0.018 to –0.011; $p < 0.001$) and recovery (β = 0.028; 95% CI, 0.011–0.015; $p < 0.001$) trend with a breakpoint albumin of 2.14 days (SD = 0.47 d) at 9.44 days (SD = 5.03 d) in survivors but did not find such two-phase trend in nonsurvivors (Table 1 and Fig. 1*B*). Compared with the COVID-19 cohort, albumin measurements in the sepsis-induced ARDS cohort were less frequent (**Supplemental Fig. 1**, http://links.lww.com/CCX/A863).

The sensitivity analysis excluding patients with an albumin infusion included 79 nonsurvivors and 197 survivors. This population had similar trends in albumin trajectory compared with our primary analysis (**Supplemental Table 1** and **Supplemental Fig. 2**, http://links.lww.com/CCX/A863).

DISCUSSION

We defined two phases of alterations in albumin levels during the course of COVID-19 critical illness. Albumin fell rapidly following admission in our COVID-19 cohort regardless of outcome; however, albumin recovery predicted clinical improvement in critical COVID-19. Interestingly, the deterioration, nadir, and recovery

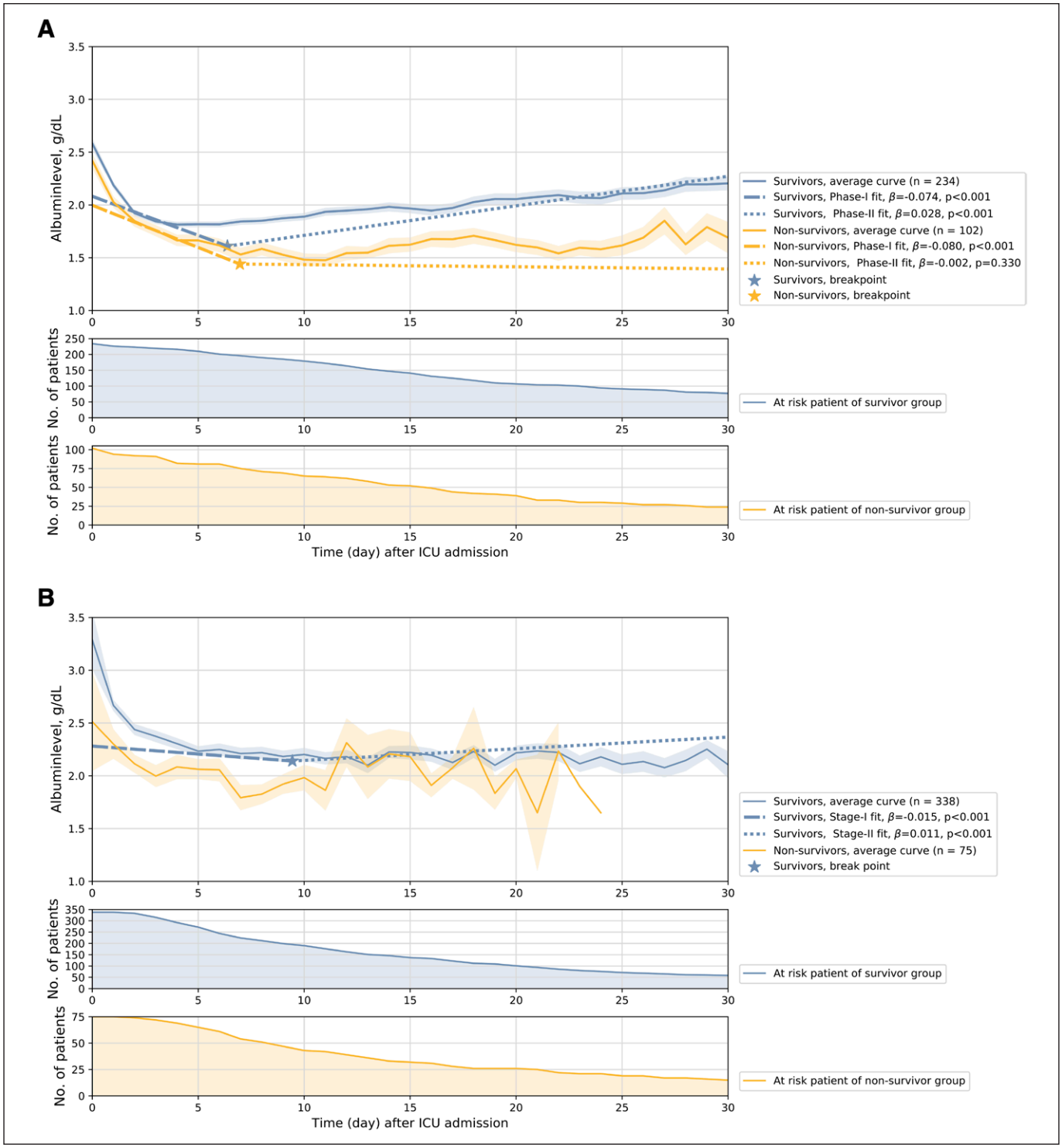

Figure 1. Illustration of albumin trajectories. **A**, Albumin trajectories (averaged trajectories and two-phase linear mixed-effects model estimated trajectories) of nonsurvivors and survivors of the critically ill coronavirus disease 2019 cohort. **B**, Albumin trajectories (averaged) of nonsurvivors and survivors of the sepsis-induced acute respiratory distress syndrome cohort.

of albumin in our COVID-19 cohort were more pronounced compared with our large sepsis-induced ARDS cohort. While a nadir and recovery were seen in our sepsis-induced ARDS survivors, these findings were subtle. Our albumin kinetic findings in COVID-19 are similar to prior research from several decades ago evaluating general critical illness (10) and more recent research on community-acquired bacteremia in

relatively healthy patients (11). It is more likely that albumin recovery represents improvement in vascular permeability given the time course of improvement rather than the resolution of illness-induced catabolism that has been seen in COVID-19 (1), but this cannot be definitively evaluated in this observational data (12).

The lack of clear albumin recovery in our sepsis-induced ARDS may be due to premorbid conditions that increase susceptibility to ARDS in the modern era outside of pandemic. Indeed, our COVID-19 patients had a lower burden of malignancy, chronic liver disease, kidney disease, and cancer compared with our sepsis population. However, the lack of clear albumin recovery in the sepsis-induced ARDS cohort may be related to unobserved confounding and secular changes in care over the past decade. Indeed, our sepsis-induced ARDS results are similar to the control group in a more recent trial of albumin resuscitation for sepsis published in 2014 (13). Albumin measurements were sparse in the sepsis-induced ARDS cohort, which may introduce noise in the identification of a break point in this population. We also did not account for albumin transfusion in this population, but our results were notable in that we did not see marked recovery patterns in this cohort, and our cohort was derived after data highlighting that albumin resuscitation is not preferred in sepsis (13). It is worth noting that albumin recovery in COVID-19 may reflect the relatively healthy population effected by the pandemic despite accepted narratives (14).

CONCLUSIONS

The changes in albumin associated with COVID-19 are more transient compared with sepsis-associated ARDS. Serum albumin normalized in survivors despite extended critical care interventions and highlights the potential for patient recovery following a protracted course of severe COVID-19.

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Drs. Su, Wang, and Schenck conceived of the study. Ms. Hoffman, Dr. Sanchez, Dr. Siempos, Dr. Schenck, created the data sources and developed case definitions. Dr. Su, Ms. Hoffman, Dr. Xu, Dr. Wang, and Dr. Schenck did the data analysis. Drs. Su and Schenck wrote the article, and all authors critically edited the final article and approved.

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