Comparing Clinical Features and Outcomes in Mechanically Ventilated Patients with COVID-19 and Acute Respiratory Distress Syndrome

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Abstract

Rationale: Patients with severe coronavirus disease (COVID-19) meet clinical criteria for the acute respiratory distress syndrome (ARDS), yet early reports suggested they differ physiologically and clinically from patients with non–COVID-19 ARDS, prompting treatment recommendations that deviate from standard evidence-based practices for ARDS.

Objectives: To compare respiratory physiology, clinical outcomes, and extrapulmonary clinical features of severe COVID-19 with non–COVID-19 ARDS.

Methods: We performed a retrospective cohort study, comparing 130 consecutive mechanically ventilated patients with severe COVID-19 with 382 consecutive mechanically ventilated patients with non–COVID-19 ARDS. Initial respiratory physiology and 28-day outcomes were compared. Extrapulmonary manifestations (inflammation, extrapulmonary organ injury, and coagulation) were compared in an exploratory analysis.

Results: Comparison of patients with COVID-19 and non–COVID-19 ARDS suggested small differences in respiratory compliance, ventilatory efficiency, and oxygenation. The 28-day mortality was 30% in patients with COVID-19 and 38% in patients with non–COVID-19 ARDS. In adjusted analysis, point estimates of differences in time to breathing unassisted at 28 days (adjusted subdistributional hazards ratio, 0.98 [95% confidence interval (CI), 0.77–1.26]) and 28-day mortality (risk ratio, 1.01 [95% CI, 0.72–1.42]) were small for COVID-19 versus non–COVID-19 ARDS, although the confidence intervals for these estimates include moderate differences. Patients with COVID-19 had lower neutrophil counts but did not differ in lymphocyte count or other measures of systemic inflammation.

Conclusions: In this single-center cohort, we found no evidence for large differences between COVID-19 and non–COVID-19 ARDS. Many key clinical features of severe COVID-19 were similar to those of non–COVID-19 ARDS, including respiratory physiology and clinical outcomes, although our sample size precludes definitive conclusions. Further studies are needed to define COVID-19–specific pathophysiology before a deviation from evidence-based treatment practices can be recommended.

Keywords: COVID-19; ARDS; physiology; outcomes

Coronavirus disease (COVID-19) causes hypoxic respiratory failure via severe lung injury. Most patients with severe COVID-19 meet clinical criteria for acute respiratory distress syndrome (ARDS), defined by hypoxemia and bilateral opacities on chest radiographs without evidence of left-sided cardiac dysfunction (1). Yet early reports suggested that the respiratory physiology among patients with severe COVID-19 might differ from that of non–COVID-19 ARDS, reflecting distinct pathophysiology, and thus should be managed differently (2, 3). In addition, early reports suggested greater mortality among mechanically ventilated patients with COVID-19 than historic ARDS cohorts (4–6). The question of whether severe COVID-19 represents "atypical ARDS" or even non-ARDS pathophysiology has been a major source of controversy (7–9).

In addition, numerous extrapulmonary clinical features have been identified as abnormal in COVID-19, which prompted widespread variation in routine intensive care unit (ICU) management. Patients with COVID-19 have been described as hyperinflammatory, exhibiting a "cytokine storm," prompting empiric and unproven use of potent, targeted immune modulators (e.g., interleukin-6 inhibition via monoclonal antibodies) (10, 11). Patients with COVID-19 have been described as hypercoagulable, with disordered indices of coagulation, prompting widespread escalation of routine ICU anticoagulation practices, even including empiric administration of thrombolytic therapy (12, 13). Finally, mechanically ventilated patients with COVID-19 develop high rates of extrapulmonary organ injury, prompting suggestions that conventional ARDS ventilator strategies may compromise patient hemodynamics and perpetuate multiorgan failure (3, 9, 14, 15). Some authors have even recommended deviating from standard ARDS evidence-based management strategies in severe COVID-19 (3, 9, 16), although others have strongly cautioned against such strategies (17, 18).

Yet these clinical features—variable respiratory mechanics, hyperinflammation, hypercoagulability, and extrapulmonary organ injury—are common among critically ill patients without COVID-19, including patients with ARDS. No study to date has systematically compared all of these clinical features of COVID-19 with a cohort of patients with non–COVID-19 ARDS; the disease-specific pathophysiologic features of severe COVID-19 have yet to be elucidated. We

performed a retrospective cohort study comparing patients with COVID-19 who received invasive mechanical ventilation with historical control subjects with ARDS from the same tertiary care center, hypothesizing that there would be no large differences between groups in these key clinical features.

Methods

Study Design
We performed a single-center retrospective cohort study. We studied consecutive adult patients (age $\geq$18 yr) with COVID-19 requiring invasive mechanical ventilation who were admitted between March 1 and June 31, 2020. All patients were observed 28 days after the onset of invasive mechanical ventilation. A CONSORT diagram is provided in Figure E1 in the online supplement. COVID-19 was diagnosed using real-time reverse transcriptase–polymerase chain reaction for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We excluded patients who were transferred for extracorporeal membrane oxygenation or initiated on invasive ventilation before the date of transfer. We excluded patients who lacked documentation in the electronic medical record of 1) height and weight, 2) arterial oxygen pressure (Pa_{O_2})/fraction of inspired oxygen ($F_{I_{O_2}}$) ratio (or arterial oxygen saturation [Sa_{O_2}]/$F_{I_{O_2}}$ ratio [19] if no arterial blood gas was obtained), or 3) static lung compliance measurement (all within the first 24 h of invasive mechanical ventilation).

We compared patients with COVID-19 with consecutive adult patients with ARDS not caused by COVID-19 admitted between January 1, 2016, and December 31, 2017, at the same center. Portions of this cohort have been described in previous studies (20, 21). ARDS was determined using formal *post hoc* adjudication by critical care–trained physicians using the Berlin Criteria as previously described (20). The additional inclusion and exclusion criteria were the same as the COVID-19 cohort.

Measurements
We collected baseline demographic data, including age, sex, self-reported race, height, and weight for all patients. Median values of $Pa_{O_2}/F_{I_{O_2}}$ ratio (or $Sa_{O_2}/F_{I_{O_2}}$ ratio), oxygenation index (or oxygen saturation index if no arterial blood gas was obtained [22]), and ventilatory ratio (23) were

calculated from the electronic health record during the first 24 hours of mechanical ventilation. All values of static lung compliance measured at the same positive end-expiratory pressure (PEEP) were also collected during the first 24 hours and the median value was determined. The highest sequential organ failure assessment (SOFA) score over the first 24 hours of mechanical ventilation was determined. We also extracted laboratory values from the electronic health record closest to the initiation of invasive mechanical ventilation, all within 48 hours of intubation. Analyses were not adjusted for multiplicity and thus should be considered exploratory.

Comparing Pulmonary Physiology and Mechanics
We compared lung compliance, ventilatory ratio, and oxygenation index before and after matching patients based on age, sex, body mass index (BMI), and the initial PEEP. Patients were matched on these characteristics because they may have an effect on respiratory mechanics independent of ARDS or COVID-19. We performed coarsened exact matching to compare these physiologic parameters in a 1:1 matched subgroup. Coarsened exact matching is a commonly used matching approach in which exact matching is performed after first "coarsening" the data (24, 25). For example, BMI is first coarsened into meaningful subgroups based on user-defined cut points or a default binning method, and then exact matches are made within subgroups. Additional matching details are described in the online supplement and matching results are shown in Table E1. We compared median physiologic variables in the unmatched and matched cohorts and performed quantile regression to estimate 95% confidence intervals (CIs) of differences in medians.

Comparing Clinical Outcomes
We compared time to breathing unassisted from mechanical ventilation before 28 days, which is measured from the first to the last time the patient received invasive mechanical ventilation during the hospitalization. We plotted a time-to-event curve for the time to breathing unassisted from mechanical ventilation before 28 days. To account for the competing risk of death, patients who died before Day 28 were assigned more than 28 days of invasive mechanical ventilation. We also determined patient status at 28 days, which included death, still hospitalized receiving

invasive mechanical ventilation, hospitalized but breathing unassisted, and discharged. Because our institution collects death data after discharge for some patients, if there was a record that the patient died within 28 days of invasive mechanical ventilation, but after discharge, they were included as a death.

To compare time to breathing unassisted in an adjusted analysis, we fit a competing risk survival model with death as competing risk and reported the subdistributional hazards ratio (SHR). We adjusted for age, sex, self-reported race, BMI, and maximum SOFA score during the first 24 hours of mechanical ventilation. We did not adjust for measures of severity of gas exchange (e.g., oxygenation index) as these may be in the causal pathway between COVID-19 or ARDS and death. To compare 28-day mortality, we fit a log binomial model adjusting for the same covariates. To estimate adjusted mortality rates, we calculated the average marginal effect in each group after fitting the model.

Comparing Laboratory Results

Certain laboratory tests were routinely obtained in all patients with COVID-19 but not among patients with non–COVID-19 ARDS, for whom specific laboratory testing was performed based on provider discretion. This resulted in differences in missingness between groups. Median differences in laboratory results were compared in patients who had the test performed. In an additional analysis described in the online supplement, laboratory results were compared after multiple imputations (26). The missingness rates and variables used in multiple imputations are described in Table E5.

As an additional sensitivity analysis, physiologic characteristics and outcomes among patients with COVID-19 were also compared with patients with non–COVID-19 ARDS and pneumonia (as adjudicated by reviewing physicians). All statistical analysis was performed in Stata version 16.1 (STATA). The institutional review board of the University of Michigan Healthcare System (HUM00104714) approved the human study protocol and deemed that informed consent was not required.

Results

We identified 130 consecutive patients with COVID-19 who received invasive mechanical ventilation and 382 historical patients with non–COVID-19 ARDS who met all study inclusion criteria (Figure E1). The baseline characteristics of both groups are shown in Table 1. Of the mechanically ventilated patients with COVID-19, 123/130 (95%) met Berlin Criteria for ARDS as adjudicated *post hoc*. There were differences in patient age, sex, self-reported race, and BMI between groups. The median delivered tidal volume was 5.9 ml/kg predicted body weight (interquartile range [IQR], 5.2–6.9) in COVID-19 and 6.0 ml/kg predicted body weight (IQR, 5.4–6.8) in non–COVID-19 ARDS, whereas median delivered PEEP was 12 (IQR, 8,14) and 8 (IQR, 5,12) for COVID-19 and non–COVID-19 ARDS, respectively. There were 182/382 (47.6%) patients with non-COVID ARDS and 66/130 (50.7%) patients with COVID-19 who had a $Pa_{O_2}/F_{I_{O_2}}$ ratio < 100 at any point during invasive mechanical ventilation. There were 33/130 (25%) patients with COVID-19 and 9/382 (2%) patients with non–COVID-19 ARDS who received prone positioning during the hospitalization.

First, we compared respiratory physiology at the onset of invasive mechanical ventilation in patients with COVID-19 and non–COVID-19 ARDS (*see* Figure 1A and Table E2). Respiratory compliance was low in both cohorts, with only 13.1% of patients with COVID-19 and 10.5% of patients with non–COVID-19 ARDS having respiratory compliance greater than 50 ml/cm H_2O, and only 3.1% of patients with COVID-19 and 3.4% of patients with non–COVID-19 ARDS having respiratory compliance equal to or greater than 70 ml/cm H_2O (normal respiratory compliance in mechanically ventilated patients without a respiratory disease [27, 28]). The median respiratory compliance was 34.6 ml/H_2O in patients with COVID-19 and 30.0 ml/H_2O in patients with non–COVID-19 ARDS (difference: 4.6 ml/H_2O; 95% CI, 1.7 to 7.6). The median ventilatory ratio (an index of ventilatory

Table 1. Characteristics of COVID-19 and patients with non–COVID-19 acute respiratory distress syndrome who received invasive mechanical ventilation

Characteristics	COVID-19 (n = 130)	Non–COVID-19 ARDS (n = 382)
Age, median (IQR), yr	64 (56–71)	59 (45–68)
Male, n (%)	85 (65)	231 (60)
Race, n (%)		
White	49 (38)	315 (82)
Black	55 (42)	38 (10)
Other/unknown	26 (20)	29 (8)
BMI, median (IQR), kg/m²	31 (27–38)	28 (24–34)
ARDS risk factor, n (%)		
Pneumonia	—	229 (60)
Aspiration	—	82 (21)
Sepsis	—	122 (32)
Trauma	—	25 (7)
$Pa_{O_2}/F_{I_{O_2}}$ ratio, n (%)		
<100	7 (5)	25 (7)
100–200	78 (60)	220 (58)
>200	45 (35)	137 (36)
SOFA score, median (IQR)	11 (10–13)	12 (10–15)
V_T, median (IQR)	5.9 (5.2–6.9)	6.0 (5.4–6.8)
PEEP, first 24 h, median (IQR)	12 (8–14)	8 (5–12)
Plateau pressure, first 24 h, median (IQR)	25 (21–28)	23 (20–27)
Driving pressure, first 24 h, median (IQR)	11 (10–13)	13 (11–17)
Received prone positioning, n (%)	33 (25)	9 (2)
Outcomes at 28 d after mechanical ventilation		
Ventilator-free days, median (IQR)	9 (0–19)	9 (0–23)
Discharged alive, n (%)	57 (44)	176 (46)
Breathing unassisted, still hospitalized, n (%)	20 (15)	36 (9)
Invasive ventilation, n (%)	14 (11)	25 (7)
Died, n (%)	39 (30)	145 (38)

Definition of abbreviations: ARDS = acute respiratory distress syndrome; BMI = body mass index; COVID-19 = coronavirus disease; $F_{I_{O_2}}$ = fraction of inspired oxygen; IQR = interquartile range; Pa_{O_2} = arterial oxygen pressure; PEEP = positive end-expiratory pressure; SOFA = Sequential Organ Failure Assessment; V_T = tidal volume.

efficiency, which correlates with dead space [29]) was 1.35 in COVID-19 and 1.41 in non–COVID-19 ARDS (difference: −0.05; 95% CI, −0.16 to 0.05). The median oxygenation index was 10.2 in COVID-19 and 8.1 in non–COVID-19 ARDS (difference: 2.1; 95% CI, 0.9 to 3.3). After excluding patients who received prone positioning during this comparison period, results were not different (Table E2).

As patients with COVID-19 and patients with non–COVID-19 ARDS differed in age, sex, BMI, and initial delivered PEEP, all of which impact respiratory mechanics, we successfully matched a 1:1 subgroup of 82 patients with COVID-19 with 82 patients with non-COVID ARDS based on age, sex, BMI, and PEEP (Table E1). In this matched

subgroup (Figure 1B), median compliance was 32.1 in COVID-19 and 30.8 in non–COVID-19 ARDS (difference: 1.1; 95% CI, −3.6 to 5.8), median ventilatory ratio was 1.33 in COVID-19 and 1.54 in non–COVID-19 ARDS (difference: −0.21; 95% CI, −0.35 to −0.07), median oxygenation index was 9.8 in COVID-19 and 9.7 in non–COVID-19 ARDS (difference: 0.2; 95% CI, −1.9 to 2.2).

We next compared 28-day clinical outcomes among patients with COVID-19 and non–COVID-19 ARDS (Figure 2). We did not detect a difference in time to breathing unassisted in patients with COVID-19 and ARDS when accounting for death as a competing risk, in both an unadjusted analysis (SHR, 0.98 [95% CI, 0.77–1.26]) and analysis adjusting for age, sex, race, BMI, and SOFA

score (SHR, 0.97 [95% CI, 0.73–1.29]). Unadjusted mortality at 28-days was 30% in COVID-19 compared with 38% in non-COVID ARDS (risk ratio, 0.79 [95% CI, 0.59–1.06]). Adjusted 28-day mortality 36.1% in patients with COVID-19 and was 35.7% in non–COVID-19 ARDS (adjusted risk ratio, 1.01 [95% CI, 0.72–1.42]). When the analysis was limited to patients with non–COVID-19 ARDS and pneumonia as an identified risk factor, initial pulmonary physiology was similar although ventilator-free days were higher in pneumonia causing ARDS compared with COVID-19 (Table E3).

We performed an exploratory analysis to identify potential differences in systemic inflammation, extrapulmonary organ injury, and disordered coagulation among patients
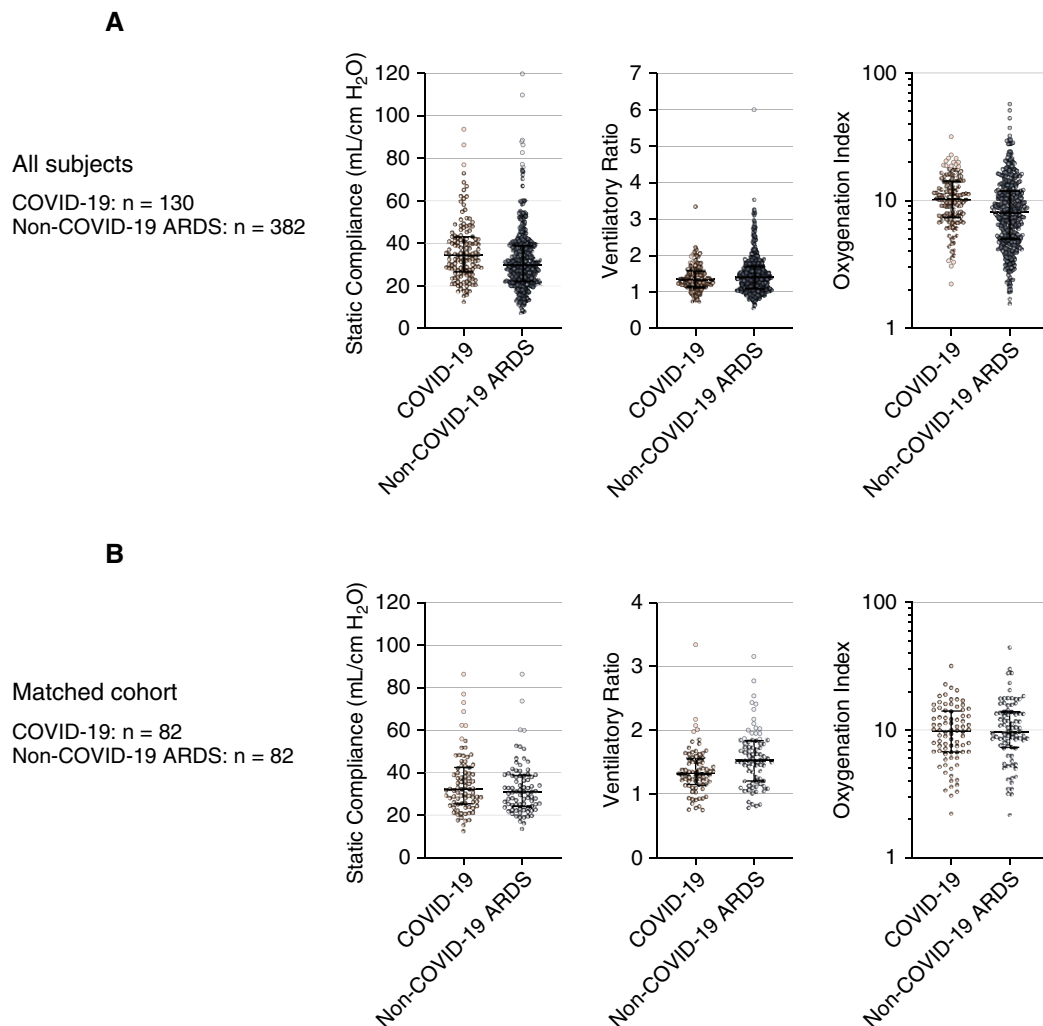

Figure 1. Respiratory physiology of mechanically ventilated patients with coronavirus disease (COVID-19) and non–COVID-19 acute respiratory distress syndrome (ARDS). Measurements were collected during the first 24 hours of invasive mechanical ventilation. The middle bar represents the median value with outer bars representing the interquartile range. (*A*) All subjects with COVID-19 and non–COVID-19 ARDS. (*B*) Matched subgroup based on age, sex, body mass index, and administered positive end-expiratory pressure.

with COVID-19 and patients with non–COVID-19 ARDS with laboratory results performed (Figure 3 and Table E4). Indices of systemic inflammation and extrapulmonary organ injury were largely similar in patients with COVID-19 and patients with non–COVID-19 ARDS at the initiation of mechanical ventilation. Total white blood cell count was lower in patients with COVID-19 (8.9 K/μl [IQR, 6.7–11.3] than in patients with non–COVID-19 ARDS (12.2 K/μl [IQR, 7.1–18]). This difference was reflected in measured neutrophil counts, which were 7.5 K/μl [IQR, 5.3–9.6] among patients with COVID-19 versus 9.6 K/μl [IQR, 5.2–14.7] among patients with non–COVID-19 ARDS. COVID-19 and non–COVID-19 ARDS did not have detectable differences in lymphocyte count or nonspecific indices of systematic inflammation (erythrocyte sedimentation rate and C-reactive protein), although there was considerable missing data among patients with non–COVID-19 ARDS for these indices.

Procalcitonin was frequently elevated in patients with COVID-19 (0.42 ng/ml [IQR: 0.22, 1.19] but higher in non-COVID ARDS (1.33 ng/ml [IQR, 0.27–9.61]). At the time of invasive mechanical ventilation, 46% of patients with COVID-19 with a procalcitonin concentration measured (55/119) had values above the normal reference value for "high probability for bacterial infection" (≥0.50 ng/

ml), as compared with 64% (145/228) of patients with non–COVID-19 ARDS. In contrast, patients with COVID-19 and patients with non–COVID-19 ARDS did not differ in their indices of renal dysfunction (blood urea nitrogen and serum creatinine) or liver injury (aspartate transaminase and alanine transaminase) at the initiation of mechanical ventilation (Table E4).

The disordered coagulation of patients with COVID-19 may have been distinct from that of patients with non–COVID-19 ARDS. Platelet count was higher in patients with COVID-19 (206 K/μl [IQR, 175–272] versus 177 K/μl [IQR, 89–262]; difference: 28 [95% CI, 3–53]), as was fibrinogen (572 mg/dl [IQR, 474–650] versus 339 mg/dl [IQR, 227–468]). Elevated D-dimer concentrations were common in both cohorts when measured, and higher among patients with non–COVID-19 ARDS (4.9 mg/L [IQR, 2–12.5] versus 2.0 mg/L [IQR, 1.1–6.9]), although there were many missing D-dimer measurements among patients with ARDS (79%, 81/382). The analysis comparing laboratory results with missing data imputed using multiple imputations was largely similar (Table E5).

Discussion

We compared a moderate-sized series of patients with COVID-19 who received

invasive mechanical ventilation with patients with non–COVID-19 ARDS who also received invasive mechanical ventilation at the same center. We did not identify major differences between the two groups in their respiratory physiology or 28-day clinical outcomes.

Early anecdotal reports suggested that most patients with severe COVID-19 exhibit "atypical ARDS" with "near-normal respiratory system compliance," reflecting unique, non-ARDS pathophysiology (2, 3, 9, 16). Yet our findings that patients with COVID-19 have profoundly impaired respiratory mechanics, comparable to those of patients with non–COVID-19 ARDS, are aligned with numerous cohort studies now representing over 1,800 mechanically ventilated patients with COVID-19 across medical centers and continents (8, 30–40). Our results also validate several recent studies that directly compared respiratory mechanics in cohorts of patients with COVID-19 and non–COVID-19 ARDS and found no meaningful difference in respiratory system compliance or other indices of respiratory mechanics (33, 38, 39). A recently published series of 32 patients with COVID-19, which reported preserved respiratory compliance in COVID-19 compared with non–COVID-19 ARDS, was an outlier among this group (41). The findings of our single-center study should be interpreted in the context of this now
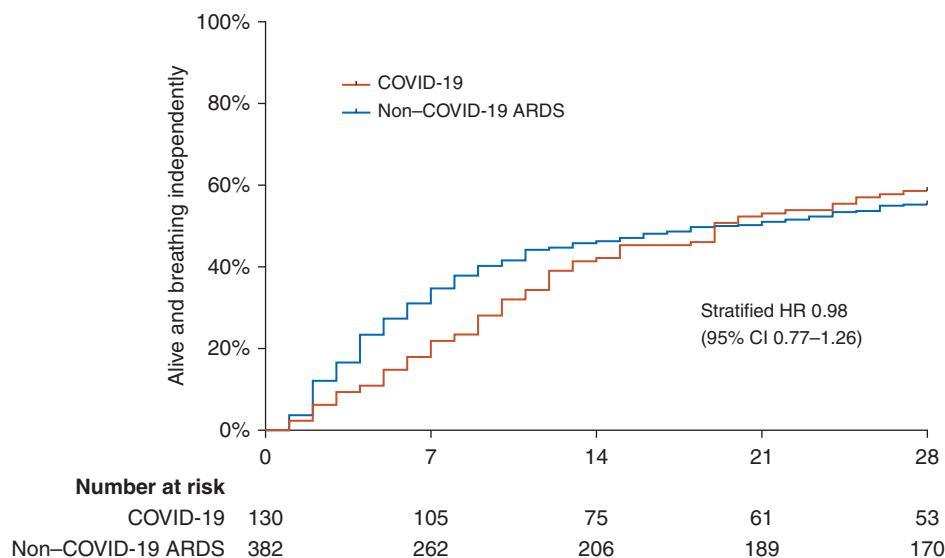

Figure 2. Comparison of time to unassisted breathing in mechanically ventilated patients with coronavirus disease (COVID-19) and non–COVID-19 ARDS. When plotting the time-to-event curve, outcomes were censored at 28 days and patients who died before 28 days were assigned 28 days of mechanical ventilation to account for death as a competing risk. The unadjusted subdistributional HR for time to breathing unassisted was calculated using a competing risk survival model, which also accounts for death as a competing risk. ARDS = acute respiratory distress syndrome; CI = confidence interval; HR = hazard ratio.

considerable literature (e.g., in a systematic meta-analysis).

Although both of our cohorts (COVID-19 and non–COVID-19 ARDS) had considerable physiologic heterogeneity, very few patients in either cohort had "near-normal" respiratory compliance (27, 28). In fact, the respiratory compliance of our COVID-19 cohort (34.6 ml/H$_2$O) was nearly identical to that of the 4,188-patient cohort used to derive and validate the Berlin Definition of ARDS (34.0 ml/H$_2$O) (1) or that of recent clinical trials of patients with severe ARDS (e.g., the PROSEVA trial, 35 ml/H$_2$O [42]). Although authors have conjectured that impaired respiratory compliance is a temporally late feature of COVID-19 lung injury, with patients initially presenting with preserved compliance (3, 9, 16), four

studies comprising over 600 mechanically ventilated patients with COVID-19 have reported serial measurements of respiratory compliance (8, 34–36), none finding any temporal trend toward decreased compliance after initiation of mechanical ventilation. A recent meta-analysis of three studies also found no correlation between duration of symptoms and respiratory compliance in patients with COVID-19 (33, 43). Although our confidence intervals exclude large differences in physiologic measurements across COVID-19 and non–COVID-19 ARDS cohorts, the range of possible differences supported by our compliance data could correspond to a 2–4% difference in predicted mortality based on recent work in ARDS cohorts (44). Taken together, our study and other large series do not support

the claim that patients with COVID-19 exhibit unique or atypical respiratory mechanics compared with other causes of ARDS.

The 28-day mortality rate of 30% among our COVID-19 cohort contrasts starkly with initial reports describing very high mortality among mechanically ventilated patients with COVID-19 (88–97%) (4, 45). This discrepancy is at least partly explained by the administrative censoring used in early studies, in which only patients with an outcome of death or discharge were analyzed at the time of study reporting, excluding many other patients still hospitalized. In contrast, we restricted our analysis to patients with COVID-19 who were observed at least 28 days after the onset of invasive mechanical ventilation. Both our clinical outcomes and our ventilator management (assessed in terms
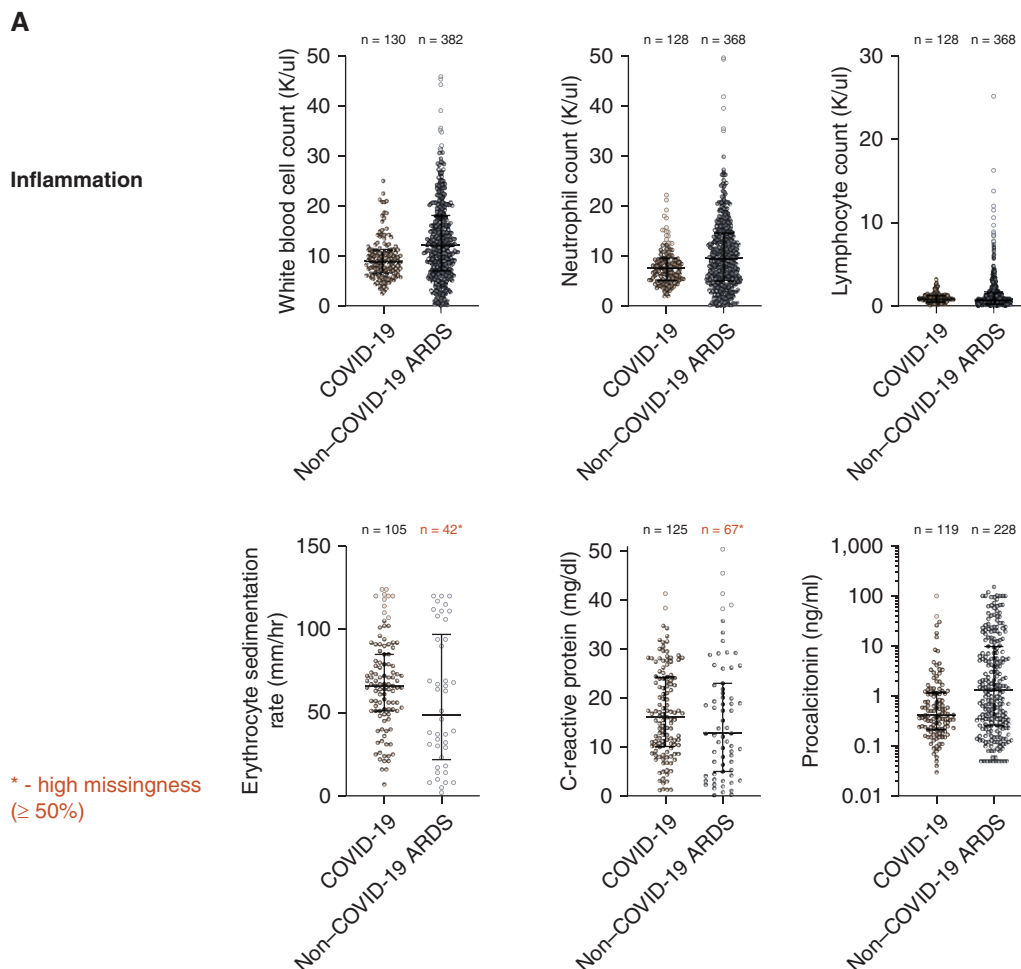

Figure 3. Extrapulmonary clinical features in mechanically ventilated patients with coronavirus disease (COVID-19) and non–COVID-19 acute respiratory distress syndrome (ARDS). (A–C) Comparison of indices of inflammation (A), extrapulmonary organ injury (B), and coagulation (C) were performed using measurements performed within 48 hours of invasive mechanical ventilation initiation. The middle bar represents the median value with outer bars representing the interquartile range. ALT = alanine transaminase; AST = aspartate transaminase.

of lung-protective ventilation and PEEP strategies) were comparable to those of patients with non–COVID-19 ARDS, similar to reports at other centers. These data do not support the widespread

speculation that conventional, evidence-based ventilator strategies for ARDS may cause harm in COVID-19 due to the purportedly unique pathophysiology of the disease (3, 14, 15).

We observed considerable heterogeneity among patients with COVID-19, both in their respiratory physiology and in their extrapulmonary disease manifestations. The heterogeneity of respiratory physiology (in
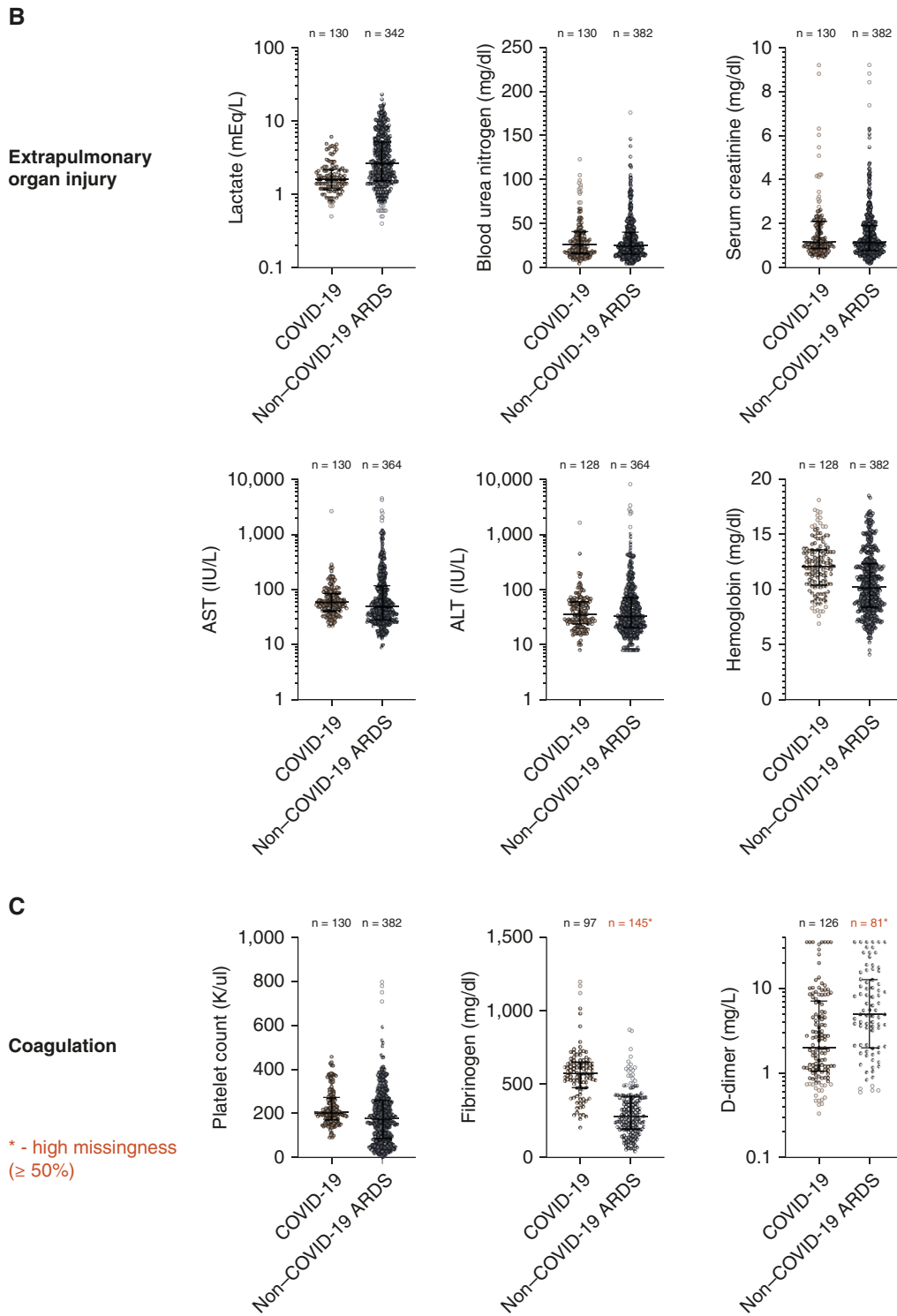

Figure 3. (Continued).

terms of both severity of lung injury and respiratory mechanics) was comparable to that of patients with non–COVID-19 ARDS, a surprising finding given that whereas COVID-19 is a pathogen-mediated *disease*, ARDS is a *syndrome* arising from highly divergent underlying etiologies. Given the well-described heterogeneity of ARDS, there have been multiple recent efforts to identify more uniform ARDS subgroups, such as by etiology (46), chest imaging findings (47), and blood biomarkers reflecting hyperinflammatory or hypoinflammatory subphenotypes (48–50). Two recent reports have confirmed the presence of subphenotypes among critically ill patients with COVID-19 that parallel those observed in non–COVID-19 ARDS (51) and sepsis (52). The observation that patients with severe COVID-19 still exhibit considerable heterogeneity suggests that clustering patients with ARDS by etiology (e.g., COVID-19) may not, by itself, be a sufficient strategy for identifying homogenous subgroups. Other underlying sources of biologic variation (e.g., genetic (53, 54), metabolomic (55, 56), and microbiologic (57–59) variation across patients) should be explored to identify clinically, prognostically, and therapeutically distinct subgroups.

Our study found that many extrapulmonary clinical features of severe COVID-19 are common among patients with non–COVID-19 causes of ARDS. Although early reports identified features purportedly specific to SARS-CoV-2 pathogenesis, these studies only compared patients with COVID-19 to reference ranges derived from healthy subjects. As an example, early reports noted immune dysfunction in severe COVID-19, manifesting with lymphopenia (60) and reflecting a supposed "cytokine storm." (10) Yet our study found similar frequency and severity of lymphopenia and nonspecific indices of systemic inflammation in patients with COVID-19 and non–COVID-19 ARDS. Systemic concentrations of inflammatory cytokines are actually lower in COVID-19 than in other causes of ARDS (11, 61), and the clinical efficacy of cytokine inhibition in COVID-19 patients has been conflicting (62–67). Taken together, these data underscore the critical importance of rigorously testing early pathophysiologic hypotheses before modifying clinical practice.

Similarly, early speculation blamed inappropriate mechanical ventilation, rather than SARS-CoV-2 infection, for the high rates of extrapulmonary organ injury observed in patients with severe COVID-

19 (3, 14, 15, 68). Yet our data suggest that extrapulmonary organ injury both is common among patients with COVID-19 at the time of intubation and may be comparable in frequency to that of non–COVID-19 ARDS. Although our data suggest that the pattern of discorded coagulation may be distinct among patients with COVID-19 (with higher platelet and fibrinogen values than non–COVID-19 ARDS patients), elevated D-dimer concentrations (which have been used in patients with COVID-19 to justify an escalation of anticoagulation regimens and even empiric thrombolysis [12, 13]) are extremely common when tested in patients with non–COVID-19 ARDS. Although we are confident that COVID-19–specific features of pathogenesis will be identified, our study underscores the importance of basing inferences on adequately powered cohorts with appropriate control arms, as opposed to underpowered, uncontrolled, and anecdotal experience (7). We emphasize that our single-center study should be interpreted in the context of the now considerable published literature of mechanically ventilated patients with COVID-19 (e.g., via meta-analysis or systematic review). Specifically, the high percentage of missing data in our comparison of coagulation parameters is an important source of bias, and these comparisons are no more than exploratory.

Limitations
The current study has several limitations. Because patients were analyzed at a single center, they were all treated under largely standardized institutional practices, which may strengthen the between-group comparisons. However, the non–COVID-19 ARDS cohort was managed during a different time period than the COVID-19 cohort; thus, some important variation in clinical practice was observed (e.g., use of prone positioning). In addition, the racial demographics of our COVID-19 and non–COVID-19 ARDS cohorts differed, attributable to a high number of emergency department–to–emergency department transfers from a nearby urban center during the COVID-19 surge. Although the study's single-center nature may also limit generalizability, both the respiratory physiology and clinical outcomes of our COVID-19 cohort were similar to those of other recent well-powered COVID-19 cohorts (8, 30–40), suggesting it is likely representative

of patients with severe COVID-19. We analyzed data recorded in the electronic medical record, which introduces variation in availability and reliability of recorded measurements and precludes analysis of respiratory parameters not routinely recorded. Other practice changes during the COVID-19 surge at our institution also prevented reliable comparison of venous thromboembolic events between groups. Although our patients without COVID-19 were studied over a 2-year period, our patients with COVID-19 were studied over a single 4-month period, introducing a potential influence of seasonality. Comparison of some extrapulmonary features of disease was limited by missing laboratory values for many patients without COVID-19. Although these comparisons were robust to multiple imputations, we emphasize that this analysis is exploratory and may be confounded by other factors in clinician ordering practices.

Conclusions
Within the limits of our sample size, we identified only small differences in respiratory physiology between patients with COVID-19 and non–COVID-19 ARDS. Clinical outcomes were also similar between groups, although the smaller sample size of this analysis precludes more definitive conclusions. Many key clinical features of COVID-19 (hyperinflammation, hypercoagulability, and extrapulmonary organ injury) are also common in non–COVID-19 ARDS. Although disease-specific features of SARS-CoV-2 pathogenesis will surely be elicited, we found no physiologic evidence that lung injury from COVID-19 falls outside of the heterogenous spectrum of ARDS arising from other etiologies. Further studies are needed to define COVID-19–specific clinical features before deviation from evidence-based treatment practices can be recommended. ∎

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