2 Liu X, Liu X, Xu Y, Xu Z, Huang Y, Chen S, *et al*. Ventilatory ratio in hypercapnic mechanically ventilated patients with COVID-19–associated acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;201:1297–1299.
3 Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;201:1299–1300.
4 Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, *et al*. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. *Am J Respir Crit Care Med* [online ahead of print] 29 Apr 2020; DOI: 10.1164/rccm.202004-1163LE.
5 Henderson WR, Chen L, Amato MBP, Brochard LJ. Fifty years of research in ARDS: respiratory mechanics in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2017;196:822–833.
6 Sinha P, Fauvel NJ, Singh S, Soni N. Ventilatory ratio: a simple bedside measure of ventilation. *Br J Anaesth* 2009;102:692–697.
7 Sinha P, Calfee CS, Beitler JR, Soni N, Ho K, Matthay MA, *et al*. Physiologic analysis and clinical performance of the ventilatory ratio in acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2019;199:333–341.
8 Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, *et al*.; COVID-19 Lombardy ICU Network. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA* 2020;323:1574–1581.
9 Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. *JAMA* [online ahead of print] 24 Apr 2020; DOI: 10.1001/jama.2020.6825.
10 Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, *et al*.; LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016;315:788–800.
11 Moss M, Ulysse CA, Angus DC; National Heart, Lung, and Blood Institute PETAL Clinical Trials Network. Early neuromuscular blockade in the acute respiratory distress syndrome: reply. *N Engl J Med* 2019;381:787–788.
12 Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.
13 Manthous CA, Hall JB, Kushner R, Schmidt GA, Russo G, Wood LD. The effect of mechanical ventilation on oxygen consumption in critically ill patients. *Am J Respir Crit Care Med* 1995;151:210–214.

Subphenotyping Acute Respiratory Distress Syndrome in Patients with COVID-19: Consequences for Ventilator Management

To the Editor:

Guidance on the best provision of care for patients with coronavirus disease (COVID-19) is urgently needed. Recently a strong argument in defense of an evidence-based approach was made in *AnnalsATS* (1), and we fully support the given line of reasoning. Most patients in the intensive care unit (ICU) with severe COVID-19 meet the criteria for acute respiratory distress syndrome (ARDS), and proven therapies for ARDS not related to COVID-19 are likely effective in these patients as well. However, ARDS is known to be a heterogeneous syndrome. Over the past decade, several biological, physiological, and morphological subphenotypes have been identified that may predict treatment effects and can be used as treatable traits (2). For example, patients with a focal lung morphology seem to respond better to prone positioning, but their lungs are not as recruitable as those of patients with a nonfocal lung morphology (3).

It has been postulated that patients with COVID-19–related ARDS can develop typical ARDS (recently called "H type," characterized by high elastance, high shunt, and high lung weight) or have an atypical presentation (recently called "L type," characterized by low elastance, low shunt, and low lung weight) (4). As with the abovementioned morphological subphenotypes, some investigators have speculated that these subphenotypes require different ventilator strategies. Patients with H-type ARDS may benefit from lower tidal volumes and higher positive end-expiratory pressure (PEEP), and patients with L-type ARDS may benefit from higher tidal volumes and lower PEEP (5).

Several steps have to be taken before subphenotype-directed treatment can be implemented in clinical practice (6). The ultimate test would be a head-to-head comparison of subphenotype-directed treatment with standard of care in a randomized controlled trial. But before this step can be considered, it is important to validate the basic assumptions underlying the subclassification of patients. We hypothesized that patients with a low elastance (i.e., with a high respiratory system

Table 1. Patient characteristics

N	38
Age, yr, mean (SD)	61.11 (8.18)
Sex, *n* (%)	
Male	26 (68.5)
Female	12 (31.6)
Days of symptoms, median (IQR)	8.00 (5.00–12.00)
PEEP, cm H_2O, median (IQR)	10.00 (9.00–12.00)
Driving pressure cm H_2O, median (IQR)	10.50 (7.25–12.75)
Plateau pressure cm H_2O, median (IQR)	20.50 (17.00–23.00)
Tidal volume, ml, mean (SD)	423.68 (73.46)
Pa_{O_2}/FI_{O_2}, mm Hg, mean (SD)	131.84 (47.92)
Compliance, ml/cm H_2O, mean (SD)	48.96 (24.45)
Severity CT, %, median (IQR)	62.5 (50–75)
Nonfocal morphology, *n* (%)	30 (78.9)

Definition of abbreviations: CT = computed tomography; FI_{O_2} = fraction of inspired oxygen; IQR = interquartile range; Pa_{O_2} = arterial oxygen tension; PEEP = positive end-expiratory pressure; SD = standard deviation.

compliance [Crs]) would also show little consolidation on chest computed tomography (CT) images, and vice versa, that patients with high elastance (i.e., low Crs) would also show much consolidation on chest CT images.

We conducted a retrospective analysis of the first 70 patients with suspected COVID-19 who were admitted to our ICU. Chest CT is performed in all hospitalized patients with suspected COVID-19. We had chest CT images for 38 patients with proven COVID-19 (54%) (Table 1), as the other patients were transferred from other hospitals to our ICU or previously had a CT scan that supported the diagnosis of COVID-19 pneumonia. Crs was calculated shortly after intubation, during neuromuscular blockade (tidal volume/driving pressure). The CT scan was performed directly after intubation and before transport to our ICU. We estimated the percentage consolidated area by summing the areas with a density of more than −500HU and expressing it as a quartile fraction (0%, 25%, 50%, 75%, or 100%). Areas with this density are known to reflect poorly or nonaerated lung tissue (7) and account for approximately <25% of lung tissue in the L-phenotype and approximately 75% in the H-phenotype (4). Lung morphology was classified as focal or nonfocal as described previously (8). We did not perform a quantitative CT analysis at this point in time because it would have required segmentation of the CT scans, which takes hours of manual labor per scan to complete; however, a semiquantitative assessment of the percentage of affected lung ought to be sufficient to distinguish between the extremes of the spectrum.

Seventeen patients (45%) had a Crs below 40 ml/cm H_2O, which has been suggested as a cutoff (9), and seven patients (18%) had minor parenchymal involvement (Figure 1). There was no relation between Crs and poorly aerated or nonaerated lung tissue (regression coefficient, +0.13% per ml/cm H_2O; 95% confidence interval, −0.17 to +0.42; $P = 0.39$). Most patients had a nonfocal lung morphology ($n = 30$, 79%). Patients with a nonfocal lung morphology had more parenchymal involvement ($P = 0.0065$) but did not have lower Crs ($P = 0.72$) than patients with focal lung morphology.

Based on these preliminary data, we conclude that compliance and an estimation of lung weight do not correlate in patients with COVID-19–related ARDS. Most patients could not be classified as either the H- or L-subphenotype, but showed mixed features. Patients frequently showed extensive parenchymal involvement and a nonfocal morphology on chest CT imaging, which might suggest recruitable lung tissue. The Crs was similar to that reported in other cohorts of patients with COVID-19 (10–12) and with ARDS not related to COVID-19. For example, the mean Crs was between 40 and 50 ml/cm H_2O in the LUNG-SAFE (Large Observational Study to Understand the

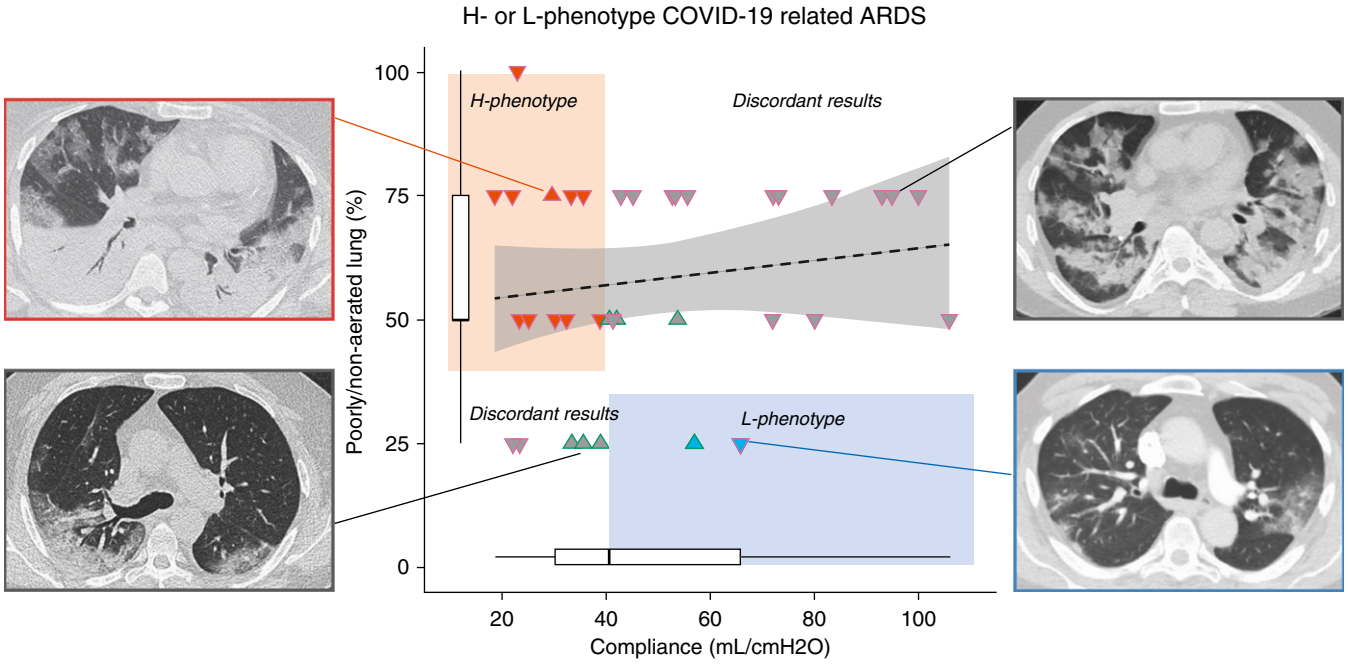

Figure 1. Association between compliance of the respiratory system (Crs) and percentage of affected lung parenchyma. *x*-axis: Crs; *y*-axis: percentage of lung that is poorly aerated or nonaerated, expressed semiquantitatively as quartiles. The boxplots indicate the distribution of the variables on the *x*- and *y*-axes. The red area and solid red symbols indicate patients with a consistent H-phenotype. The blue area and solid blue symbols indicate patients with a consistent L-phenotype. The solid gray symbols correspond to patients with a discordant phenotype. Indicative computed tomography images for each area are shown on both sides. Crs is not associated with an increase in poorly aerated/nonaerated lung tissue estimated by semiquantitative analysis in quartiles. Regression coefficient for Crs: +0.13% per ml/cm H_2O (95% confidence interval, −0.17 to +0.42; $P = 0.39$). Two patients met the criteria for the L-phenotype and 12 patients met the criteria for the H-phenotype, leaving 24 patients (63%) with discordant results and an unclear phenotype allocation. Most patients had a nonfocal lung morphology ($n = 30$, 79%) rather than a focal lung morphology ($n = 8$, 21%). ARDS = acute respiratory distress syndrome; COVID-19 = coronavirus disease.

Global Impact of Severe Acute Respiratory Failure) study and other observational and interventional studies (7, 13, 14).

Our observations are limited by the absence of a quantitative CT analysis. However, given the urgent need for data, we used a semiquantitative surrogate that should capture the distinctions that were described in previous publications. Another limitation is that we did not perform a formal evaluation of recruitability by performing CT imaging at different PEEP levels. We should acknowledge that the semiquantitative evaluation of CT images at a single level of PEEP is not even available for most clinicians caring for patients with COVID-19, and that most physicians will therefore resort to using the Crs when these subphenotypes are applied in clinical practice. Our data clearly indicate that the lung compliance alone does not correlate with the amount of lung parenchyma that is affected. Although our sample size was small, there is no suggestion in our data that the "H-/L-phenotyping" schema accurately describes our patients with COVID-19.

This study represents the first independent test of the proposed subphenotypes of COVID-19–related ARDS, and highlights that the features of the H- and L-subphenotypes are not mutually exclusive. We also validated the existence of heterogeneity in lung morphology known from non–COVID-19–related ARDS. We need data-driven approaches to evaluate the existence of treatable traits to improve patient-tailored care. Until these data become available, an evidence-based approach extrapolating data from ARDS not related to COVID-19 is the most reasonable approach for ICU care (1).

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References

1 Rice TW, Janz DR. In defense of evidence-based medicine for the treatment of COVID-19 ARDS. *Ann Am Thorac Soc* [online ahead of print] 22 Apr 2020; DOI: 10.1513/AnnalsATS.202004-325IP.
2 Prescott HC, Calfee CS, Thompson BT, Angus DC, Liu VX. Toward smarter lumping and smarter splitting: rethinking strategies for sepsis and acute respiratory distress syndrome clinical trial design. *Am J Respir Crit Care Med* 2016;194:147–155.
3 Constantin J-M, Jabaudon M, Lefrant J-Y, Jaber S, Quenot J-P, Langeron O, *et al*.; AZUREA Network. Personalised mechanical ventilation tailored to lung morphology versus low positive end-expiratory pressure for patients with acute respiratory distress syndrome in France (the LIVE study): a multicentre, single-blind, randomised controlled trial. *Lancet Respir Med* 2019;7: 870–880.
4 Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, *et al*. COVID-19 pneumonia: different respiratory treatment for different phenotypes? *Intensive Care Med* [online ahead of print] 14 Apr 2020; DOI: 10.1007/s00134-020-06033-2.
5 Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. *JAMA* [online ahead of print] 24 Apr 2020; DOI: 10.1001/jama. 2020.6825.
6 Sinha P, Calfee CS. Phenotypes in acute respiratory distress syndrome: moving towards precision medicine. *Curr Opin Crit Care* 2019;25: 12–20.
7 Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, *et al*. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med* 2006;354:1775–1786.
8 Constantin JM, Grasso S, Chanques G, Aufort S, Futier E, Sebbane M, *et al*. Lung morphology predicts response to recruitment maneuver in patients with acute respiratory distress syndrome. *Crit Care Med* 2010;38:1108–1117.
9 Gattinoni L, Chiumello D, Rossi S. COVID-19 pneumonia: ARDS or not? *Crit Care* 2020;24:154.
10 Gattinoni L, Coppola S, Cressoni M, Busana M, Rossi S, Chiumello D. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med* 2020;201:1299–1300.
11 Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, *et al*. Covid-19 in critically ill patients in the Seattle region: case series. *N Engl J Med* 2020:382:2012–2022.
12 Ziehr DR, Alladina J, Petri CR, Maley JH, Moskowitz A, Medoff BD, *et al*. Respiratory pathophysiology of mechanically ventilated patients with COVID-19: a cohort study. *Am J Respir Crit Care Med* [online ahead of print] 29 Apr 2020; DOI: 10.1164/rccm.202004-1163LE.
13 Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, *et al*.; LUNG SAFE Investigators; ESICM Trials Group. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315:788–800.
14 Brower RG, Matthay MA, Morris A, Schoenfeld D, Thompson BT, Wheeler A; Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000;342:1301–1308.