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Hospital Variation in Management and Outcomes of Acute Respiratory Distress Syndrome Due to COVID-19

OBJECTIVES: To describe hospital variation in use of "guideline-based care" for acute respiratory distress syndrome (ARDS) due to COVID-19.

DESIGN: Retrospective, observational study.

SETTING: The Society of Critical Care Medicine's Discovery Viral Infection and

RESPIRATORY ILLNESS UNIVERSAL STUDY COVID-19 REGISTRY.

PATIENTS: Adult patients with ARDS due to COVID-19 between February 15, 2020, and April 12, 2021.

INTERVENTIONS: Hospital-level use of "guideline-based care" for ARDS including low-tidal-volume ventilation, plateau pressure less than 30 cm H_2O, and prone ventilation for a Pao_2/Fio_2 ratio less than 100.

MEASUREMENTS AND MAIN RESULTS: Among 1,495 adults with COVID-19 ARDS receiving care across 42 hospitals, 50.4% ever received care consistent with ARDS clinical practice guidelines. After adjusting for patient demographics and severity of illness, hospital characteristics, and pandemic timing, hospital of admission contributed to 14% of the risk-adjusted variation in "guideline-based care." A patient treated at a randomly selected hospital with higher use of guideline-based care had a median odds ratio of 2.0 (95% CI, 1.1–3.4) for receipt of "guideline-based care" compared with a patient receiving treatment at a randomly selected hospital with low use of recommended therapies. Median-adjusted inhospital mortality was 53% (interquartile range, 47–62%), with a nonsignificantly decreased risk of mortality for patients admitted to hospitals in the highest use "guideline-based care" quartile (49%) compared with the lowest use quartile (60%) (odds ratio, 0.7; 95% CI, 0.3–1.9; $p = 0.49$).

CONCLUSIONS: During the first year of the COVID-19 pandemic, only half of patients received "guideline-based care" for ARDS management, with wide practice variation across hospitals. Strategies that improve adherence to recommended ARDS management strategies are needed.

KEY WORDS: acute respiratory distress syndrome; COVID-19; low-tidal-volume ventilation; prone ventilation; severe acute respiratory syndrome coronavirus-2; Viral Infection and Respiratory Illness Universal Study

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G uidelines for the medical treatment of severe COVID-19 infection have evolved over the first years of the pandemic (1), but standards for the ventilator management of the acute respiratory distress syndrome (ARDS) that complicates COVID-19 are well-established (2). Unfortunately, despite cumulative evidence from randomized controlled trials in ARDS demonstrating the mortality benefit of low-tidal-volume ventilation (low Vt) (3), defined as 4–8 mL/kg predicted body weight, lower inspiratory pressure targets (plateau pressure [Pplat] less than 30 cm H_2O) (4), as well as prone ventilation for moderate-severe ARDS (5, 6), adoption of these interventions for

non-COVID-19 ARDS prior to the COVID-19 pandemic was poor (7–11).

During the early months of the COVID-19 pandemic, some questioned the applicability of established ventilator management strategies for COVID-19 ARDS ("CARDS") (12), whereas others affirmed the generalizability of evidence-based critical care to COVID-19 (13). Recent studies attempting to quantify the impact of these debates on clinical practice identify higher rates of adherence to low Vt within a single health system (14) or country (15) than that seen in non-COVID-19 ARDS. These data underscore an opportunity to identify patient- and hospital-level factors associated with adoption of use of low Vt, among other guideline-recommended interventions, and to assess their impact on patient outcomes.

We sought to characterize international hospital-level variation in use of ARDS management strategies with established mortality benefit within the Society of Critical Care Medicine's Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS) COVID-19 registry and to expand the current literature on variation in use of ARDS management strategies by identifying hospital- and patient-level factors associated with use. We hypothesized that: 1) CARDS management strategies would vary across hospitals and 2) better adherence to guideline-recommended ventilator management strategies would be associated with improved CARDS mortality.

MATERIALS AND METHODS

Study Population

We performed a retrospective cohort study of adults (greater than or equal to 18 yr), hospitalized with confirmed COVID-19 infection and receiving invasive mechanical ventilation for ARDS between February 15, 2020, and April 12, 2021, using the VIRUS registry. ARDS was defined by receipt of mechanical ventilation and a ratio of partial pressure of arterial oxygen divided by F_{IO_2} (Pa_{O_2}/F_{IO_2} ratio) less than 300 during their hospitalization (**Fig. 1**). Consistent with Berlin definition of ARDS, all patients included received greater than or equal to 5 cm H_2O of positive end-expiratory pressure. Although nearly 90% of patients with reported chest radiograph had bilateral infiltrates, due to high missingness of chest radiograph reporting (45%), notoriously poor reliability of chest radiograph interpretation for ARDS determination (16), and known pathologic and clinical association of severe COVID-19 infection with diffuse alveolar damage and ARDS (17), Berlin criteria of bilateral opacities on imaging were not required for study inclusion. Hospitals that enrolled fewer than 10 total patients in the registry or completed less than 80% of outcomes data for their registry were excluded to stabilize estimates of ARDS management strategies and restrict data to hospitals engaged in high-quality data entry.
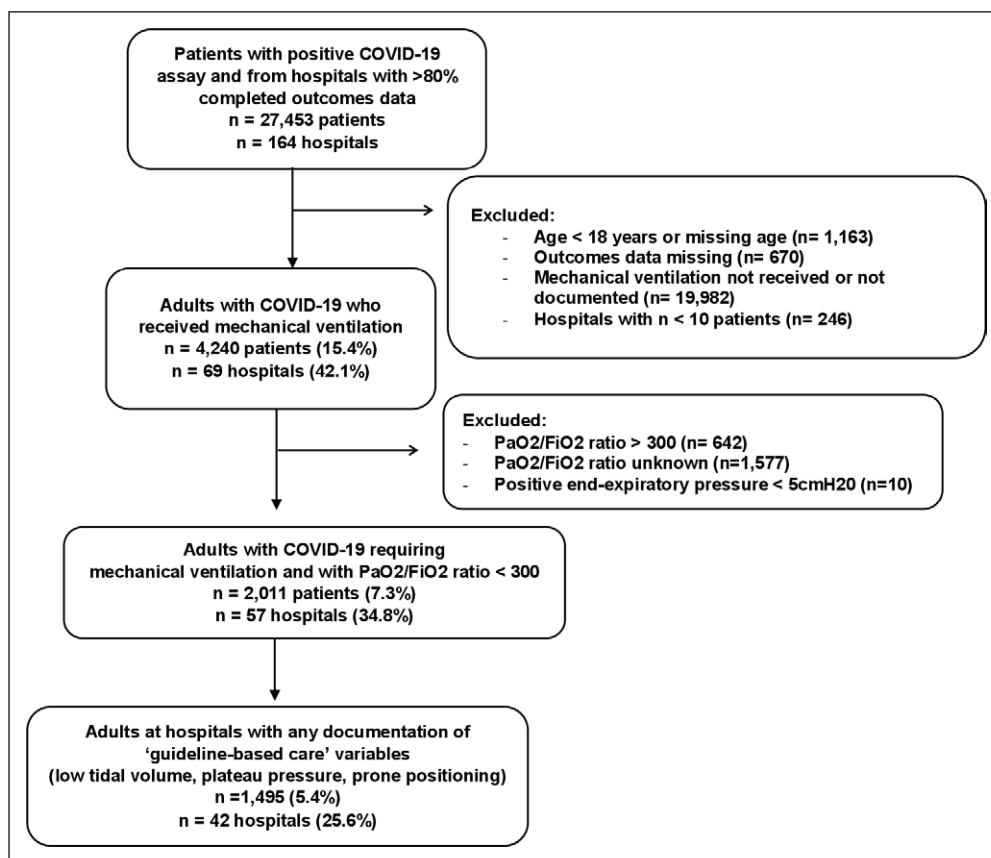
Figure 1. Cohort assembly of adults with acute respiratory distress syndrome due to COVID-19.

Data were collected from day of hospital admission or the date first available if admission data were missing. Patients with missing tidal volume, Pplat, or prone positioning data were excluded from the model assessing variation in use of "guideline-based care."

Outcomes

The primary outcome of interest was hospital-level variation in use of "guideline-based care" for ARDS management. "Guideline-based care" was determined by worst Pao_2/Fio_2 (P/F) ratio; among those with a P/F ratio between 100 and 300, use was defined as receipt of low Vt of 4–8 cc per kg ideal body weight and Pplat below 30 cm H_2O. For patients with a P/F ratio less than 100, "guideline-based care" was additionally defined by receipt of prone positioning. Due to daily data entry into our database, the exact temporal relationship between patient illness severity and use of guideline-based ARDS management strategies is unknown. However, aligning with our primary focus on hospital-level practice patterns, our analysis captures whether a patient meeting criteria for ARDS ever received all the care strategies recommended for this diagnosis (low Vt, Pplat less than 30, and prone positioning for P:F less than 100). To address the possibility of patients dying before having a chance to receive all aspects of "guideline-based care," a sensitivity analysis was performed among patients with greater than 1 day of mechanical ventilation. Additionally, to address the possibility that patients receiving extracorporeal membrane oxygenation (ECMO) may be more likely to receive low Vt, an additional sensitivity analysis was performed excluding patients with receipt of ECMO. For our exploratory analyses of the association of: 1) hospital-level use of "guideline-based care" and overall inhospital patient mortality and 2) hospital-level use of "guideline-based care" and patient discharge status to home, hospitals were grouped into quartiles of risk-adjusted use of "guideline-based care" based on the percentage of patients receiving recommended management strategies at each hospital (0–24%, 25–49%, 50–74%, and 75–100%), due to the nonlinear association of use with outcomes. Descriptive use of neuromuscular blockade (i.e., paralytics), inhaled pulmonary vasodilators, and ventilator strategies including airway pressure release ventilation is additionally reported.

Covariates

We adjusted models for potential confounding variables including patient characteristics (i.e., patient age, race, sex, body mass index [BMI], comorbid conditions, and admission code status), patient severity of illness (i.e., worst Sequential Organ Failure Assessment score and P/F ratio during admission), and hospital characteristics (i.e., geographic location where hospital is located [United States vs international], hospital type [academic vs nonacademic], ICU type [medical/COVID vs other], hospital capacity [overcapacity vs under capacity], and nurse-to-patient staffing ratios [low vs high]). Due to limitations of anonymity required for the VIRUS registry, further delineation of specific countries was not available. Academic hospitals were defined by hospitals at which residents and/or medical student were the first contact to provide ICU care. Overcapacity was defined by the number of COVID-19 patients at any given time outnumbering the number of ICU beds available at the hospital, and low nurse-to-patient staffing ratios were defined by greater than two patients per nurse (18, 19). We additionally adjusted models for time of admission during the pandemic (early [before July 1, 2020] vs later [after July 1, 2020]) based on the availability of data from clinical trials for the management of COVID-19. Mortality assessments were adjusted for corticosteroid use given the survival benefit of dexamethasone in severe COVID-19 infection (20).

Data Source

The Society of Critical Care Medicine Discovery VIRUS COVID-19 registry (21, 22) (NCT04323787) was approved by the Mayo Clinic (20-002610) and Boston University (H-40009) institutional review boards with waiver of informed consent due to the deidentified nature of the registry and the lack of interaction between study personnel, clinicians, and patients. Following local institutional review board approval and signed data use agreement, study data were recorded and managed using the Research Electronic Data Capture system (REDCap) (23). REDCap is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry, 2) audit trails for tracking data manipulation and export procedures, 3) automated export procedures for seamless data

downloads to common statistical packages, and 4) procedures for importing data from external sources. The study was determined to be exempt from Institutional Review Board. The study is registered on Clinicaltrials.gov: NCT04323787.

Statistical Analysis

Dichotomous and categorical variables are reported as counts and percentages. Continuous variables are reported using means with sd or median with interquartile range (IQR) based on the distribution. Trends of use of ARDS ventilator management strategies, associated measures of lung compliance, and patient and hospital characteristics were compared across quartiles of use of "guideline-based care" using the Cochran-Armitage test for categorical variables and F test on linear regression for continuous variables. Multilevel random effects modeling was performed, with each hospital included as a random intercept and above covariates as fixed effects, in order to determine the hospital risk-adjusted rates of "guideline-based care" for ARDS management. Variation in use of "guideline-based care" for ARDS management was described by the model intraclass correlation coefficient and the median odds ratio (24). After adjusting for patient- and hospital-level factors, the intraclass correlation coefficient summarizes the variation in guideline-based ARDS management attributable to the hospital itself. When considering an individual receiving care at a randomly selected hospital with higher versus lower use of "guideline-based care," the median odds ratio represents the median increase in the odds of receiving "guideline-based ARDS care" at that higher use hospital. For the exploratory analyses of use of "guideline based care" on inhospital patient mortality and patient discharge status to home, hospitals were grouped into quartiles of risk-adjusted "guideline-based ARDS management" as the exposure of interest due to the nonlinear association of use with outcomes and convergence difficulties with random effects spline-based models.

Missing data were not imputed as they could not be considered to be missing completely at random. For missing covariate data due to the lack of entry by participating sites, as opposed to pending outcomes data of patients still hospitalized, complete case analysis was used to minimize introduction of "incomplete outcome data bias" (25). All tests were two-sided and conducted using a significance level of 0.05. Statistical analyses were conducted using statistical analysis software, SAS (Version 9.4, Cary, NC).

RESULTS

Patient and Hospital Characteristics

Fourteen hundred and ninety-five mechanically ventilated adults with COVID-19 infection and ARDS met criteria for inclusion in the study (Fig. 1). Over half the cohort (801; 54%) had severe ARDS as defined by P/F < 100. Median age was 64 (IQR, 54–72), two-thirds of patients (67%) were male, 654 (43.7%) were White and 298 (33.2%) were Black, and median BMI was 29.4 (IQR, 26–35). Patients were managed predominantly at U.S. hospitals (73%) with an academic affiliation (63%), and the majority had a full code status (93%) (**Table 1**). Distributions of academic hospital affiliation ($p = 0.02$), nurse-to-patient ratio ($p = 0.007$), and hospital capacity strain ($p = 0.001$) differed across quartiles of "guideline-based care" (Table 1).

ARDS Ventilator Management Strategies

Among patients cared for at hospitals where "guideline-based care" variables were reported (hospital $n = 42$) (Fig. 1), quartiles of risk-adjusted hospital-level use of "guideline-based care" were identified, and ARDS management strategies were compared (**Table 2**). Low Vt was used in the management of 79% of patients, inspiratory Pplat less than 30 cm H_2O was achieved for 74% of patients, and more than half of patients with severe ARDS (62.3%) were managed with prone positioning. The distribution of use of these "guideline-based care" ARDS management strategies differed significantly across hospital quartiles of use ($p < 0.0001$; $p < 0.0001$; $p = 0.001$, respectively). Nearly half of patients were managed with adjunctive strategies including paralytics (56.3%) and inhaled pulmonary vasodilators (48.3%) with similarly significant differences across hospital quartiles of use ($p < 0.0001$ and $p = 0.002$, respectively). Use of these adjunctive strategies was lowest at hospitals in the second to lowest quartile of "guideline-based care" use (Table 2).

Hospital Variation in Use of "Guideline-Based Care" for ARDS

In a complete case analysis of patients where all "guideline-based care" covariates were available (patient

TABLE 1.
Patient and Hospital Characteristics Stratified by Hospital Quartiles of Use of Guideline-Based Care[a]

Characteristics	Overall	Q1 (0–24th %)	Q2 (25–49th %)	Q3 (50–74th %)	Q4 (75–100th %)	p[b]
n (%)	1,495 (100)	383 (25.6)	366 (24.5)	335 (24.5)	411 (27.5)	
Patient characteristics						
Admission month						
March–June, 2020	528 (39.8)	143 (55.4)	92 (25.2)	187 (57.5)	106 (28.0)	0.0002
July 2020–April 2021	799 (60.2)	115 (44.6)	273 (74.8)	138 (42.5)	273 (72.0)	0.0002
Age (yr), median (IQR)	64 (54–72)	65 (53–72)	65 (55–73)	64 (54–71)	63 (53–72)	0.36
Sex						
Male	998 (66.8)	260 (68.1)	231 (63.1)	243 (72.5)	264 (64.2)	0.75
Female	496 (33.2)	122 (31.9)	135 (36.9)	92 (27.5)	147 (35.8)	0.75
Intersex	< 5	< 5	< 5	< 5	< 5	-
Race						
White Caucasian	654 (43.7)	134 (35.0)	214 (58.5)	134 (40.0)	172 (41.8)	0.81
Black or African American	298 (19.9)	50 (13.1)	67 (18.3)	87 (26.0)	94 (22.9)	< 0.0001
Asian American	156 (10.4)	57 (14.9)	34 (9.3)	48 (14.3)	17 (4.1)	< 0.0001
Other	387 (25.9)	142 (37.1)	51 (13.9)	66 (19.7)	128 (31.1)	0.30
Hispanic						
Hispanic	287 (19.2)	113 (29.5)	62 (16.9)	44 (13.1)	68 (16.5)	< 0.0001
Non-Hispanic	1,208 (80.8)	270 (70.5)	304 (83.1)	291 (86.9)	343 (83.5)	< 0.0001
Height (cm), median (IQR)[c]	170 (162–176)	170 (164–177)	168 (161–175)	170 (163–176)	168 (160–178)	0.66
Weight (kg), median (IQR)[c]	85 (73–99	84 (75–96	85 (73–101	84 (75–97	85 (71–104	0.05
Predicted weight (kg), median (IQR)[c]	64.1 (56.9–70.7)	65.9 (56.9–71.4)	63.8 (54.7–70.7)	65.9 (56.9–70.5)	62.0 (55.2–70.7)	0.29
Body mass index (kg/m²), median (IQR)[c]	29.4 (26.0–34.7)	29.2 (25.8–33.3)	29.5 (26.0–35.2)	29.4 (25.4–34.7	29.7 (26.3–35.3)	0.06
Comorbidities						
Coronary artery disease	235 (15.7)	80 (20.9)	78 (21.3)	30 (9.0)	47 (11.4)	< 0.0001
Congestive heart failure	184 (12.3)	63 (16.4)	55 (15.0)	27 (8.1)	39 (9.5)	0.0003
Chronic pulmonary disease	297 (19.9)	19 (5.0)	200 (54.6)	32 (9.6)	46 (11.2)	0.006
Asthma	153 (10.2)	26 (6.8)	72 (19.7)	21 (6.3)	34 (8.3)	0.23
Chronic kidney disease	215 (14.4)	51 (13.3)	77 (21.0)	37 (11.0)	50 (12.2)	0.10
Chronic dialysis	36 (2.4)	13 (3.4)	10 (2.7)	5 (1.5)	8 (1.9)	0.12
Diabetes	572 (38.3)	155 (40.5)	149 (40.7)	119 (35.5)	149 (36.3)	0.11
Liver disease	54 (3.6)	4 (1.0)	32 (8.7)	8 (2.4)	10 (2.4)	0.63
HIV/AIDS	15 (1.0)	5 (1.3)	2 (0.5)	5 (1.5)	3 (0.7)	0.69
Current smoker	61 (4.2)	12 (3.3)	6 (1.7)	22 (6.6)	21 (5.2)	0.03
Former smoker	349 (24.2)	40 (11.0)	129 (37.4)	79 (23.7)	101 (24.9)	0.005

(*Continued*)

TABLE 1. (*Continued*).
Patient and Hospital Characteristics Stratified by Hospital Quartiles of Use of Guideline-Based Care[a]

	Overall	Q1 (0–24th %)	Q2 (25–49th %)	Q3 (50–74th %)	Q4 (75–100th %)	p[b]
Full code status at admission	1,397 (93.4)	348 (90.9)	361 (98.6)	320 (95.5)	368 (89.5)	0.16
Maximum Sequential Organ Failure Assessment score, median (IQR)[c]	9 (6–11)	9 (7–12)	9 (7–11)	8 (6–11)	9 (6–11)	0.05
Worst Pao_2/Fio_2 ratio during admission						
< 300	145 (9.7)	41 (10.7)	25 (6.8)	22 (6.6)	57 (13.9)	0.13
< 200	549 (36.7)	165 (43.1)	77 (21.0)	133 (39.7)	174 (42.3)	0.14
< 100	801 (53.6)	177 (46.2)	264 (72.1)	180 (53.7)	180 (43.8)	0.02
Hospital characteristics						
Hospital type[a]						
Academic	861 (62.8)	257 (71.6)	105 (32.4)	259 (79.7)	240 (66.3)	0.02
ICU type[a]						
Medical or COVID ICU	1,055 (77.0)	359 (100)	324 (100)	245 (75.4)	127 (35.1)	< 0.0001
Hospital capacity[a]						
Overcapacity	880 (64.2)	245 (68.2)	266 (82.1)	115 (35.4)	254 (70.2)	0.001
Nurse staffing level[a]						
Low nurse to patient ratio	370 (27.0)	73 (20.3)	58 (17.9)	168 (51.7)	71 (19.6)	0.007
Hospital site[a]						
United States	1,097 (73.4)	259 (67.6)	344 (94.0)	154 (46.0)	340 (82.7)	0.72

IQR = interquartile range.

[a]Guideline-based care = low tidal volume and plateau pressure < 30 for 100 < Pao_2/Fio_2 (P/F) < 300 and additionally by prone positioning for P/F < 100. Academic hospital refers to hospital where resident and/or medical student is the first contact to provide ICU care, other ICU represents pediatric or mixed ICU, overcapacity refers to number of patients at peak of COVID greater than number of ICU beds, low nurse to patient ratio represents greater than two patients per nurse, and high nurse to patient ratio represents one to two patients per nurse and hospital site represents United States vs international hospitals.

[b]p represents significance of trend from quartile of hospitals with the lowest use of guideline-based care (Q1) up to quartile of hospitals with highest use of guideline-based care (Q4).

[c]Covariate missingness (% missing, n missing): height (13%, n = 265), weight (13%, n = 258), predicted weight (15%, n = 308), body mass index (13%, n = 271), and Sequential Organ Failure Assessment (5%, n = 105).

n = 739; hospital n = 31), the rate of "guideline-based care" for ARDS varied between hospitals with a median hospital-level rate of (50%; IQR, 45–59%; range, 29–71%) (**Fig. 2**). After adjusting for patient demographic, and severity of illness characteristics and pandemic timing, hospital of admission contributed to 20% of the risk-adjusted variation in guideline-based care. The median odds ratio (MOR), which represents the median increase in the odds of a patient receiving "guideline-based" ARDS care when treated at a randomly selected hospital with practice patterns highly consistent with ARDS guidelines compared with a hospital with practice patterns less consistent with guidelines, was 2.4 (95% CI, 1.20–4.67). With the addition of hospital-level factors including academic affiliation, bed capacity, and nurse-to-patient staffing ratios, the contribution of hospital of admission to the risk-adjusted variation in use guideline-based care

TABLE 2.
Acute Respiratory Distress Syndrome Management Strategies Stratified by Hospital Quartiles of Use of Guideline-Based Care[a]

|	Overall	Q1 (0–24th %)	Q2 (25–49th %)	Q3 (50–74th %)	Q4 (75–100th %)	P[b]
Acute respiratory distress syndrome management strategies	1,495 (100)	383 (25.6)	366 (24.5)	335 (24.5)	411 (27.5)	
Tidal volume, mean (SD)[a]	7.2 (1.5)	8.1 (2.0)	7.3 (1.2)	6.9 (1.4)	6.8 (1.1)	< 0.0001
Plateau pressure (cm H_2O), median (IQR)[c]	26 (22–30)	29 (24–30)	28 (24–30)	25 (22–29)	24 (20–27)	< 0.0001
Positive end-expiratory pressure (cm H_2O), median (IQR)[a,c]	11 (8–14)	12 (10–14)	10 (8–14)	12 (10–14)	12 (10–14)	0.05
Driving pressure (cm H_2O), mean (SD)[c]	15 (6)	16 (6)	17 (5)	14 (5)	13 (6)	< 0.0001
Static compliance, mean (SD)[c]	40 (40)	44 (60)	30 (12)	40 (34)	47 (48)	0.007
Ventilator mode, n (%)						
Volume control	780 (69.5)	89 (49.7)	209 (70.6)	218 (67.7)	264 (81.0)	< 0.0001
Pressure control	129 (11.5)	52 (29.1)	10 (3.4)	58 (18.0)	9 (2.8)	0.001
Pressure support	25 (2.2)	10 (5.6)	1 (0.3)	14 (4.3)	0 (0.0)	0.12
Others	157 (14.0)	23 (12.8)	54 (18.2)	28 (8.7)	52 (16.0)	0.04
Airway pressure release ventilation[a]	89 (6.0)	30 (7.8)	30 (8.2)	14 (4.2)	15 (3.6)	0.002
Extracorporeal membrane oxygenation, n (%)[a]	115 (7.7)	38 (9.9)	20 (5.5)	33 (9.9)	24 (5.8)	0.16
Paralytics, n (%)	841 (56.3)	236 (61.6)	109 (29.8)	226 (67.5)	270 (65.7)	< 0.0001
Inhaled pulmonary vasodilators, n (%)	722 (48.3)	209 (54.6)	93 (25.4)	190 (56.7)	230 (56.0)	0.002
Prone positioning, n (%)	858 (57.4)	233 (60.8)	164 (44.8)	217 (64.8)	244 (59.4)	0.20
Prone positioning, P:F < 100	499 (62.3)	110 (62.2)	126 (47.7)	141 (78.3)	122 (67.8)	0.001
Low tidal volume (4–8 cc/kg), n (%)[c]	809 (79.0)	85 (53.5)	215 (77.1)	246 (85.4)	263 (88.3)	< 0.0001
Plateau pressure < 30 cm H_2O, n (%)[c]	737 (74.4)	64 (50.7)	181 (67.5)	217 (79.8)	265 (86.9)	< 0.0001
Guideline-based care, n (%)[a,c]	458 (50.4)	19 (14.1)	100 (39.1)	146 (59.8)	193 (70.7)	< 0.0001

IQR = interquartile range.

[a]Tidal volume = tidal volume (mL)/predicted weight (kg). Guideline-based care = low tidal volume and plateau pressure < 30 for 100 < Pao_2/Fio_2 (P/F) < 300 and additionally by prone positioning for P/F < 100.

[b]p represents significance of trend from quartile of hospitals with lowest use of guideline-based care (Q1) up to quartile of hospitals with highest use of guideline-based care (Q4).

[c]Covariate missingness (% missing, n missing): positive end-expiratory pressure (40%, n = 815), driving pressure (52% missing = n = 1,036), static compliance (52%, n = 1052), low tidal volume (32%, n = 471), plateau pressure (34%, n = 505), and guideline-based care (39%, n = 587).
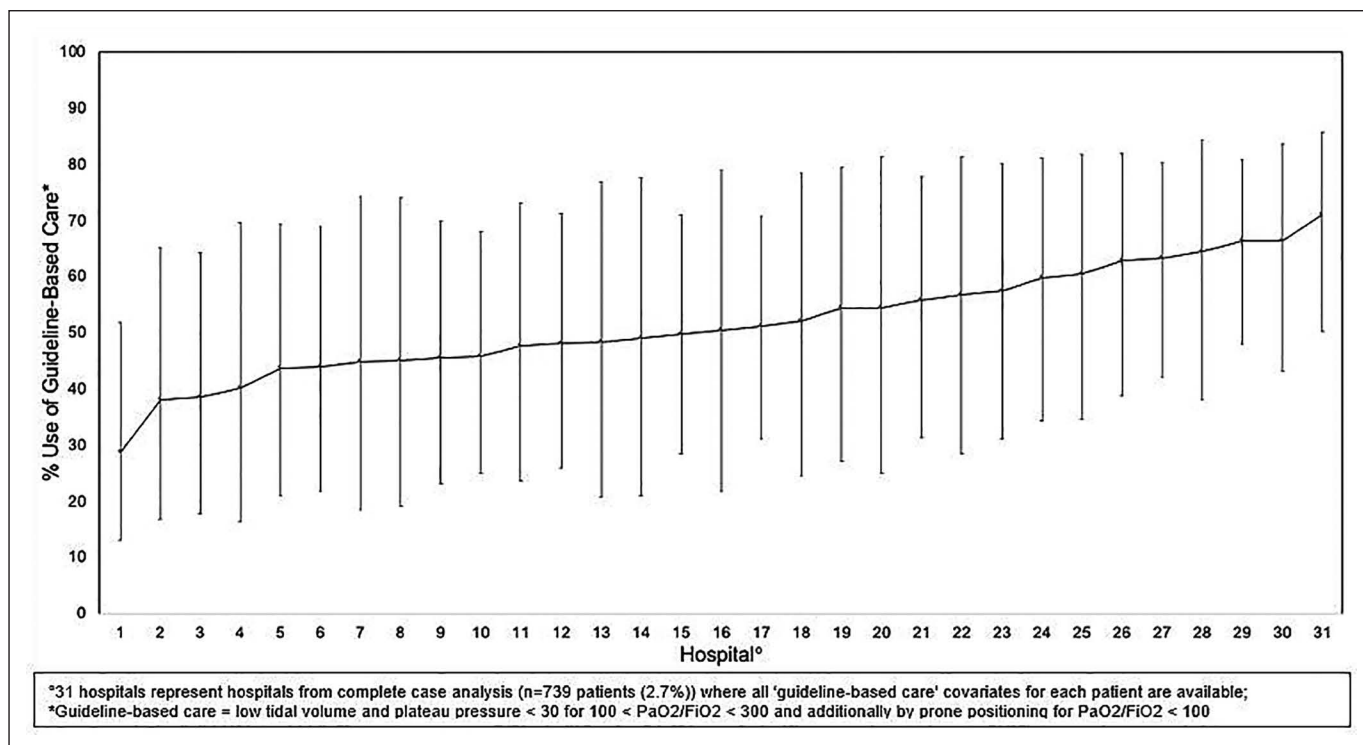
Figure 2. Multivariable-adjusted variation in hospital-level use of guideline-based care for patients with acute respiratory distress syndrome acute respiratory distress syndrome, defined by receipt of low tidal volume ventilation (4–8-cc/kg ideal body weight) and plateau pressure below 30 cm H_2O for $100 < Pao_2/Fio_2$ ratio < 300 and additionally by prone positioning for Pao_2/Fio_2 ratio < 100 with adjustment for patient and hospital characteristics.

decreased from 20% to 14% with an MOR of 2.0 (95% CI, 1.15–3.43).

Factors Associated With Use of Guideline-Based Care

When accounting for both patient- and hospital-level factors that may explain variation in use of "guideline-based care," female sex was associated with a 53% decreased odds of receiving "guideline-based care" (OR, 0.47; 95% CI, 0.33–0.68; $p < 0.0001$), and history of chronic dialysis was associated with an 81% decreased odds (OR, 0.19; 95% CI, 0.05–0.71; $p = 0.01$) of "guideline-based care" (**Table 3**). ARDS severity was also significantly associated with use of "guideline-based care" ($p < 0.0001$). Pplat targets less than 30 cm H_2O were least commonly achieved among patients with severe ARDS where receipt of "guideline based care" was less likely compared with mild disease (**Supplemental Table 1**, http://links.lww.com/CCX/A920; Table 3). A smoking history was significantly associated with receipt of guideline-recommended therapies (OR, 1.76; 95% CI, 1.15–2.70; $p = 0.01$). Designated medical and/

or COVID-19 ICUs were significantly less likely to use "guideline-based care" (OR, 0.26; 95% CI, 0.12–0.56; $p = 0.001$). Hospital capacity and nurse-to-patient ratios were not associated with receipt of "guideline-based care." Compared with the early months of the pandemic, use of "guideline-based" care was similar in the later months of the pandemic (OR, 1.2; 95% CI, 0.8–1.9; $p = 0.47$) (Table 3). Results from sensitivity analyses among patients receiving mechanical ventilation for more than 1 day and excluding those who received ECMO were unchanged.

Association Between Use of Guideline-Based ARDS Care and Inhospital Mortality

Unadjusted inhospital mortality was 54%. Median-adjusted hospital-level mortality was 53% (IQR, 47–62%) with a nonsignificantly decreased risk of mortality for patients admitted to hospitals in the highest use evidence-based care quartile (49%) compared with the lowest use quartile (60%) (risk-adjusted OR for Q4 vs Q1, 0.7 [95% CI, 0.3–1.5]) (**Supplemental Table 2**, http://links.lww.com/CCX/A921). Further

TABLE 3.
Patient- and Hospital-Level Factors Associated With Use of Guideline-Based Care for Acute Respiratory Distress Syndrome Due to COVID-19

Characteristics	Guideline-Based Care;[a] Patient-Level Variable Model		Guideline-Based Care;[a] Patient- and Hospital-Level Variable Model	
	OR (95% CI)	p	OR (95% CI)	p
Age	0.99 (0.97–1.00)	0.11	0.99 (0.75–1.85)	0.09
Sex				
Male	1.00 (reference)		1.00 (reference)	
Female	0.48 (0.33–0.69)	< 0.0001	0.47 (0.33–0.68)	< 0.0001
Body mass index	0.99 (0.96–1.01)	0.49	0.99 (0.96–1.02)	0.44
Race				
White	1.00 (reference)		1.00 (reference)	
Black or African American	0.69 (0.41–1.15)	0.35	0.70 (0.41–1.19)	0.20
Asian	0.53 (0.25–1.14)		0.50 (0.23–1.05)	
Other	0.95 (0.56–1.63)		1.01 (0.59–1.74)	
Ethnicity				
Non-Hispanic	1.00 (reference)		1.00 (reference)	
Hispanic	1.21 (0.71–2.07)	0.48	1.20 (0.70–2.04)	0.51
Comorbidities				
Coronary artery disease	1.29 (0.77–2.15)	0.33	1.32 (0.79–2.20)	0.30
Congestive heart failure	1.13 (0.64–1.98)	0.67	1.19 (0.67–2.09)	0.55
Chronic pulmonary disease	1.15 (0.65–2.00)	0.63	1.20 (0.69–2.10)	0.52
Asthma	1.22 (0.71–2.10)	0.47	1.22 (0.71–2.10)	0.47
Chronic kidney disease	1.30 (0.78–2.15)	0.31	1.33 (0.80–2.21)	0.27
Chronic dialysis	0.20 (0.06–0.74)	0.02	0.19 (0.05–0.71)	0.01
Diabetes mellitus	1.05 (0.73–1.50)	0.80	1.07 (0.74–1.53)	0.73
Liver disease	0.78 (0.35–1.77)	0.56	0.78 (0.34–1.75)	0.54
HIV/AIDS	1.04 (0.22–4.99)	0.96	1.06 (0.22–5.10)	0.94
Tobacco use				
Current smoker	0.94 (0.41–2.17)	0.88	0.87 (0.38–2.04)	0.76
Former smoker	1.78 (1.16–2.72)	0.01	1.76 (1.15–2.70)	0.01
Admission code status				
Full code	1.41 (0.68–2.92)	0.35	1.49 (0.72–3.12)	0.29
Acute respiratory distress syndrome severity[a]				
P/F < 300	1.00 (reference)		1.00 (reference)	
P/F < 200	1.85 (0.88–3.86)	< 0.0001	1.91 (0.91–4.02)	< 0.0001
P/F < 100	0.69 (0.33–1.43)		0.71 (0.34–1.49)	
Maximum Sequential Organ Failure Assessment score	0.96 (0.90–1.01)	0.12	0.96 (0.90–1.01)	0.13
Admission month				
February–June 2020	1.00 (reference)			
July 2020–April 2021	1.27 (0.81–1.98)	0.30	1.18 (0.75–1.85)	0.47

(*Continued*)

TABLE 3. (*Continued*).
Patient- and Hospital-Level Factors Associated With Use of Guideline-Based Care for Acute Respiratory Distress Syndrome Due to COVID-19

Characteristics	Guideline-Based Care;[a] Patient-Level Variable Model		Guideline-Based Care;[a] Patient- and Hospital-Level Variable Model	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Hospital location				
United States	1.00 (reference)			
International	0.97 (0.38–2.51)	0.95	0.88 (0.34–2.29)	0.80
Hospital type[a]				
Nonacademic			1.00 (reference)	
Academic			2.00 (0.91–4.42)	0.09
ICU type[a]				
Other ICU			1.00 (reference)	
Medical or COVID ICU			0.26 (0.12–0.56)	0.001
Hospital capacity[a]				
Undercapacity			1.00 (reference)	
Overcapacity			1.04 (0.46–2.32)	0.93
Nurse staffing level[a]				
Low nurse to patient ratio			1.00 (reference)	
High nurse to patient ratio			1.12 (0.43–2.93)	0.81

OR = odds ratio, P/F = Pao_2/Fio_2 ratio.

[a]Guideline-based care = low tidal volume and plateau pressure < 30 for 100 < P/F < 300 and additionally by prone positioning for P/F < 100. Academic hospital refers to hospital where resident and/or medical student is the first contact to provide ICU care, other ICU represents pediatric or mixed ICU, overcapacity refers to number of patients at peak of COVID greater than number of ICU beds, low nurse to patient ratio represents greater than two patients per nurse, and nurse to patient ratio represents one to two patients per nurse.

adjustment for hospital-level factors (ICU capacity, nurse-to-patient staffing ratios, and academic affiliations) resulted in little change to effect estimates (risk-adjusted OR for Q4 vs Q1, 0.7 [0.3–1.9]). Half of patients were discharged home (risk-adjusted median 54%; IQR, 45–61%), and receipt of "guideline-based care" was not significantly associated with discharge to home (**Supplemental Table 3**, http://links.lww.com/CCX/A922).

DISCUSSION

In this multicenter, international study of 1,495 patients with ARDS due to COVID-19, only half of patients received care consistent with ARDS guidelines. Although the majority of patients received either low Vt, values of Pplat less than 30 cm H_2O, or prone ventilation for severe ARDS, combined use of these strategies among eligible patients was relatively poor. Despite established guidelines for ARDS management, we identified large practice variations in hospital-level use of guideline-recommended ARDS management strategies. After adjusting for patient characteristics and hospital resources, patients receiving care at a randomly selected hospital with practice patterns more consistent with ARDS guidelines had 2.0 times the odds of receiving these interventions compared with a patient being treated at a hospital with practice patterns less consistent with ARDS guidelines. Patients treated at hospitals with higher rates of "guideline-based care" had a nonsignificantly lower odds of mortality. These data provide important motivation to design strategies to align ARDS management with guideline recommendations for patients with COVID-19 and underscore the importance of considering hospital-level resources when evaluating capacity to adopt guidelines.

These data presented from patients with COVID-19 add novel information regarding ARDS practice patterns that can be interpreted in the context of prior surveys of intended ARDS practices among patients with COVID-19 (26) and observational studies of patients with ARDS prior to the COVID-19 pandemic. Our data demonstrate encouraging signs of relatively high use of each guideline-based management strategy for ARDS; however, variation in combined use of "guideline-based care" across hospitals highlights room for improvement. Rates of prone ventilation, which was provided to 62% of patients with severe ARDS, were double previously reported rates among patients without CARDS (i.e., 16–33%) (9). This likely reflects clinician awareness of the benefits of prone ventilation early on in the pandemic, when there were no alternate therapies with mortality benefit (27). Although overall rates of use of low Vt and Pplat targets less than 30 cm H_2O were high (78.9% and 74.4%, respectively), one-third of patients with mild ARDS did not receive low Vt and Pplat targets less than 30 cm H_2O were less likely to be achieved among patients with severe ARDS. The discordance in adherence to overall "guideline-based care" among those with moderate ARDS but not severe disease seen in our study draws specific attention to patients with severe disease where adherence to Pplat targets may be particularly difficult due to poor lung compliance.

Within the highest use quartile of "guideline-based care," academic affiliations and high nurse-to-patient staffing ratios (i.e., fewer patients per nurse) may have impacted adherence to best practices. The negative association between use of "guideline-based care" and medical or COVID ICUs compared with mixed or PICUs may represent the severity of cases designated to ICUs with expertise in disease pathophysiology when hospitals are caring for patients beyond capacity or controversies as to whether COVID-19 should be managed as traditional ARDS (28). Poor adoption of "guideline-based care" among women may be informed by prior studies demonstrating lower odds of lung-protective ventilation in women, likely as a result of bias in height assessments and default tidal volumes (8, 29). Adjunctive therapies for ARDS management including paralytics and inhaled pulmonary vasodilators were used nearly as commonly as evidence-based practices, without predilection for use at low-performing "guideline-based care" hospitals, warranting further guidance of efficacy and appropriate use, specifically within the CARDS population.

Strengths of this study include evaluation of ARDS practices for patients with COVID-19 across an international sample of hospitals. Results should also be considered in the context of study limitations. First, P/F ratios used to classify severity of illness represent the most severe point in a patients' illness. Second, serial measurements of Pao_2 and Fio_2 throughout a patients' hospitalization were not available; therefore, association of ventilator management with time-varying ARDS severity may be limited. Additionally, "guideline-based care" strategies only had to be met at any time during mechanical ventilation. Daily data for each strategy were not available, so we are unable to comment on how frequently strategies were met simultaneously or separately. Fourth, categorization of continuous exposure variable of hospital-guideline base care into quartiles may lead to loss of information in the model; however, random effects spline-based models had convergence difficulties. Fifth, the impact of conservative versus liberal fluid management strategies on CARDS mortality could not be captured using this registry. Finally, residual confounding from unmeasured severity of illness may cannot be ruled out.

CONCLUSIONS

During the first year of the COVID-19 pandemic, half of patients received "guideline-based care" for ARDS management and use of "guideline-based care" varied widely across hospitals. Given the significant mortality risk associated with ARDS, efforts should focus toward identifying strategies that optimize adherence to care practices with established survival benefit.

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APPENDIX

The journal is requested to PubMed index the list of The Society of Critical Care Medicine Discovery Viral Infection and Respiratory Illness Universal Study (VIRUS): COVID-19 Registry Investigator Group: COVID-19 Registry Investigator Group as collaborative coauthors submitted along with this article: 1) Columbia: Clinica Medical SAS: Oscar Y. Gavidia, Felipe Pachon, and Yeimy A. Sanchez; 2) Egypt: Helwan University: Mohamed El Kassas, Mohamed Badr, Ahmed Tawheed, Ahmed Tawheed, and Hend Yahia; 3) Japan: Center Hospital of the National Center for Global Health and Medicine: Wataru Matsuda and Reina Suzuki; Jichi Medical University Saitama Medical Center: Reina Suzuki, Masamitsu Sanui, and Sho Horikita; Sapporo City General Hospital: Yuki Itagaki, Akira Kodate, Reina Suzuki, Akira Kodate, Yuki Takahashi, and Koyo Moriki; 4) Pakistan: Dow University Hospital: Muhammad Sohaib Asghar, Mashaal Syed, and Syed Anosh Ali Naqvi; 5) Russia: Kuban State Medical University with affiliation Territorial Hospital 2: Igor Borisovich Zabolotskikh, Konstantin Dmitrievich Zybin, Sergey Vasilevich Sinkov, and Tatiana Sergeevna Musaeva; 6) Saudi Arabia: King Saud University: Mohammed A. Almazyad, Mohammed I. Alarifi, Jara M. Macarambon, Ahmad Abdullah Bukhari, Hussain A. Albahrani, Kazi N. Asfina, and Kaltham M. Aldossary; 7) Serbia: CHC Bezanijska kosa, Belgrade: Marija Zdravkovic, Zoran Todorovic, Viseslav Popadic, and Slobodan Klasnja; University Hospital Center "Dr Dragisa Misovic-Dedinje": Predrag D. Stevanovic, Dejan S. Stojakov, Duska K. Ignjatovic, Suzana C. Bojic, Marina M. Bobos, Irina B. Nenadic, Milica S. Zaric, Marko D. Djuric, and Vladimir R. Djukic; 8) Spain: Hospital Universitario La Paz: Santiago Yus and Belen C. Martin; 9) Turkey: Marmara University: Uluhan Sili, Huseyin Bilgin, and Pinar Ay; and 10) United States of America: Allina Health (Abbott Northwestern Hospital, United Hospital, and Mercy Hospital in Minnesota): Roman R. Melamed, David M. Tierney, Love A. Patel, Vino S. Raj, Barite U. Dawud, Narayana Mazumder, Abbey Sidebottom, Alena M. Guenther, Benjamin D. Krehbiel, Nova J. Schmitz, Stacy L. Jepsen, Lynn Sipsey, Anna Schulte, Whitney Wunderlich, and Cecely Hoyt; Advocate Christ Medical Center: Kenneth W. Dodd, Nicholas Goodmanson, Kathleen Hesse, Paige Bird, Chauncey Weinert, Nathan Schoenrade, Abdulrahman Altaher, Esmael Mayar, Matthew Aronson, Tyler Cooper, Monica Logan, Brianna Miner, and Gisele Papo; Al-Amiri and Jaber Al-Ahmed Hospitals, Kuwait

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