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Implementation of Protocolized Care in ARDS Improves Outcomes

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BACKGROUND: Treatments of ARDS that improve patient outcomes include use of lung-protective ventilation, prone ventilation, and conservative fluid management. Implementation of ARDS protocols via educational programs might improve adherence and outcomes. The objective of this study was to investigate the effects of an ARDS protocol implementation on outcomes and adherence with ARDS guidelines. METHODS: This was a single-center, interventional, comparative study before and after protocol implementation. Staff education for the ARDS protocol was implemented between June 2014 and May 2015. A retrospective cohort analysis was conducted during between January 2012 and May 2014 (pre-protocol) and between June 2015 and June 2017 (post-protocol). A total of 450 subjects with ARDS were included. After propensity score matching, 432 subjects were analyzed. Of those, 330 subjects were treated after protocol implementation. RESULTS: The median (interquartile range [IQR]) plateau pressure and tidal volume over the first 3 d decreased significantly after protocol implementation (30.5 [IQR 24.2–33] vs 25.5 [IQR 21.7–30], $P = .01$ and 7.65 vs 7.4 mL/kg predicted body weight, $P = .032$, respectively). The percentage of subjects with unsafe tidal volume (> 10 mL/kg predicted body weight) decreased (14.4% vs 5.8%, $P = .02$). The percentage of subjects with safe plateau pressure (≤ 30 cm H_2O) increased (47.4% vs 76.5%, $P < .001$). PEEP deviation from the ARDSNet PEEP/F_{IO_2} table was significantly lower after the implementation. Mortality at 28 and 90 days improved after implementation (53.9% vs 41.8% and 61.8% vs 48.2%, respectively). Adjusted odds ratios for 28-d and 90-d mortality were 0.47 (95% CI 0.28–0.78) and 0.45 (95% CI 0.27–0.76), respectively. CONCLUSIONS: ARDS protocol implementation was associated with improved survival and rate of adherence. *Key words: acute respiratory distress syndrome; mechanical ventilation; gas exchange; lung protective ventilation; protocol implementation; propensity score matching.* [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

ARDS is associated with high mortality and morbidity.[1] Evolving disease is associated with severe hypoxemia that can result in multi-organ failure.[2] Hypoxemia associated with ARDS often necessitates the introduction of assorted conventional and adjunctive therapies.[3] ARDS management in the era of lung-protective ventilation revolves around strategies that extol the virtues of limiting barotrauma (ie, maintaining plateau airway pressures [P_{plat}] < 30 cm H_2O), and volutrauma (tidal volume 6–8 mL/kg predicted body weight), lung recruitment (utilization of PEEP titration and prone ventilation) and disruption of inflammatory cascade caused by ventilator-induced lung injury (neuromuscular blocking agents).[3-7]

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Use of lung-protective ventilation is associated with improved survival in ARDS.[3,4] Prone ventilation and the use of continuous neuromuscular blocking agents improve survival in patients with moderate to severe ARDS.[6,7] In contrast, the use of pulmonary vasodilators, recruitment maneuvers, PEEP, and early initiation of diuretics improves oxygenation and increases ventilator-free days without necessarily affecting survival.[3,8,9] Consequently, the mortality benefit accrued from application of extracorporeal membrane oxygenation remains limited to patients with severe ARDS who have failed conventional mechanical ventilation.[10,11] Despite extensive literature detailing the use of these strategies, significant variability exists in their application at the bedside.[12,13] This heterogeneity in the adoption and widespread application of these therapies despite ample scientific evidence can have significant impact on the outcome of patients with ARDS.[14] Lack of physician and institute expertise, concerns around potential lack of benefit, and the potential for adverse events have all been cited as significant barriers to the consistent application of these therapies.[12,13,15,16]

Protocols are dynamic guides based on the best available evidence to develop effective pathways for patient care. Studies have shown that implementation of individual protocols to ensure lung-protective ventilation strategies, conservative fluid management, and adjunctive therapies are associated with improved outcomes in patients with ARDS.[7,17,18] However, multi-dimensional protocols that advocate the institution of divergent treatment modalities in complex disease states such as sepsis,[19] delirium,[20] or standardized mechanical ventilation[14] suffer from low adherence and inconsistent impact. This lack of benefit has been attributed to protocol misalignment and impact misattribution.[21] Evidence supporting the protocolized institution of conventional and adjunctive therapies in the management of ARDS in a stepwise manner (least to most resource intensive therapies), commensurate to the degree of hypoxemia is conspicuous in its absence.

We hypothesized that the institution of a tiered protocol advocating an evidenced-based, step-up algorithm would complement the bedside clinician's expertise in ARDS management while improving patient care and outcomes. We also hypothesized that a comprehensive educational program involving caregivers in the ICU prior to the implementation of the protocol would reduce the common pitfalls associated with misalignment and misattribution that is commonplace in protocol application.

QUICK LOOK

Current knowledge

Significant variability exists in the management strategies for ARDS. This heterogeneity in the adoption and widespread application of these therapies despite ample scientific evidence may have significant impact on the outcome of patients with ARDS.

What this paper contributes to our knowledge

An ARDS management protocol associated with provider education improved adherence to evidence-based management in subjects with ARDS. Implementation of such a protocol was associated with improved survival, increased the rate of discharge home, and decreased the utilization of adjunctive and rescue interventions.

Methods

Study Setting and Patient Population

This was a before-and-after study performed at a 64-bed closed medical ICU at Cleveland Clinic main campus hospital (Cleveland, Ohio), a quaternary academic referral center, from 2012 to 2017. The study design included a pre-intervention period (January 2012 to May 2014), a washout period as the protocol was implemented, followed by an intervention period (June 2015 to June 2017), when an ARDS protocol was implemented for all patients with ARDS. We performed a retrospective analysis of prospectively screened patients with a diagnosis of ARDS based on the Berlin definition[22] from 2012 to 2017. All intubated patients admitted to our medical ICU are prospectively screened daily for the presence of ARDS for potential enrollment in research studies. We reviewed all of the screening logs for patients who met eligibility for ARDS; we also queried our electronic medical records to identify any missing patients. All patients with a diagnosis of ARDS identified from all sources were included in the cohort. The screening logs were sensitive and accounted for $>$ 90% of the included patients. This study was approved by the Cleveland Clinic institutional review board.

ARDS Protocol

A task force consisting of intensivists, respiratory therapists, pharmacists, and nurses was convened to create a protocol for the purpose of standardizing the care of patients with ARDS. Regular meetings were held by the task force to review relevant literature and discuss practical aspects of protocol implementation. The initial protocol was finalized In May 2014, and the tiered ARDS management protocol was launched in the medical ICU. The launch of this protocol was paired with extensive simulation training as well as didactic and bedside teaching related to the management of patients with ARDS over the next 6 months (through December 2014). A final document based on feedback was approved by consensus and made available online in the

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Cleveland Clinic intranet in December 2014. We utilized concepts from Gagne's sequence of instruction and learning theory for the teaching modules for the clinical teams (see the supplementary materials at http://www.rcjournal.com).[23,24] Based on this protocol, participating teams were encouraged to consider specific management interventions based on severity of hypoxemia and other mechanical ventilator parameters for any patient who met the Berlin definition for ARDS.[22] The clinical team had the option to follow or disregard any part of the protocol they felt was appropriate for the individual patient. The protocol consisted of 5 domains (see the supplementary materials at http://www.rcjournal.com): (1) Implementation of lung-protective ventilation strategies for all patients with ARDS; (2) PEEP and F_{IO_2} titration based on the third ARDSnet PEEP/F_{IO_2} table; (3) fluid conservation strategies based on the FACCT lite[17] protocol; (4) strategies to minimize asynchrony with the ventilator in the first 48 h of ARDS; (5) early (ie, within 48 h) use of adjunctive therapies (prone ventilation and neuromuscular blocking agents) in patients with moderate-to-severe ARDS ($P_{aO_2}/F_{IO_2} < 150$). Adjunctive therapies with no mortality benefit (eg, inhaled vasodilators, recruitment maneuvers, extracorporeal membrane oxygenation) or the use of prone ventilation and neuromuscular blocking agents beyond 48 h were considered to be rescue therapies (full protocol available in the supplementary materials at http://www.rcjournal.com).

Data Collection and Study Definitions

Baseline characteristics were collected on the first day that subjects met all ARDS criteria, regardless of hospital or ICU admission date. ICU-specific care, evolution of disease, mechanical ventilator parameters, co-existing organ failures, severity of illness, and adjunctive therapy use were collected through the ICU admission. The worst value for any variable in a 24-h period was collected. We determined the adherence of management in mechanical ventilation using the average settings' values from day 1 to day 3 of ARDS. We defined acute kidney injury and septic shock according to guidelines from The Kidney Disease: Improving Global Outcomes 2012 guidelines[25] and Sepsis-3 consensus definition, respectively.[26] Our primary outcome of interest was 28-d mortality. Secondary outcomes included ventilator-free days up to day 28, length of ICU and hospital stay, and all-cause mortality up to 90 d. Study data were collected and managed using REDCap.[27]

Statistical Analysis

Descriptive statistics were presented as proportions for categorical variables and mean ± SD or median [interquartile range (IQR)] for continuous variables. Proportions were compared using chi-square or Fisher exact tests, and continuous variables were compared with the Student test or the Wilcoxon rank-sum test as appropriate. Missing data of the entire cohort and subjects in the subgroup who had $P_{aO_2}/F_{IO_2} < 150$ were handled using multiple imputation to create and analyze 50 imputed data sets to complete logistic regression for propensity score matching.[28] The imputation processes included variables that were incorporated into both regression models and also included outcomes variables.[29] Calculations of missing values were done in R 3.5.2 (R Foundation, Vienna, Austria) using automatic predictor selection tool of the Multivariate Imputation by Chained Equations 3.0 package.

Propensity Score

Covariates associated with the implementation of ARDS protocol or with 28-d mortality were included in a multivariable logistic regression analysis with the implementation of the ARDS protocol as the dependent variable to determine propensity score of the implementation of ARDS protocol for each patient and each imputed data set. The independent covariates were age; body mass index; Charlson comorbidities index; Acute Physiology, Age, Chronic Health Evaluation (APACHE) III score; history of diabetes mellitus, chronic kidney disease, liver disease, or active malignancy; aspiration as a cause of ARDS; septic shock; P_{aO_2}/F_{IO_2} on day 1 and mean airway pressure on day 1; and time from intubation to hospital admission. After creating the 50 imputed data sets, we generated individual propensity score models for each data set. We averaged propensity scores for each subject and then matched propensity scores across the imputed data set. We assessed balance for the imputed data sets for each unit across imputations. Absolute values of standardized differences < 0.1 indicated sufficient balance. Appropriate reduction in the imbalance between the 2 cohorts was achieved after matching (see the supplementary materials at http://www.rcjournal.com).

Matching Procedure

For the matching method, subjects post implementation of the ARDS protocol were matched with subjects who did not receive the implementation of the ARDS protocol, using a 1:1 nearest neighbor matching procedure with replacement and a caliper width equal to 0.2 of the standard deviation of the logit of the propensity score.[30] The model estimates and standard errors were combined into a single set of results using Rubin's rules.[31]

Outcome Analysis

Logistic regression was performed to evaluate the effect of the implementation of the ARDS protocol on the 28-d and 90-d mortality, using covariates selected a priori (age, APACHE III score, Charlson comorbidity index, septic

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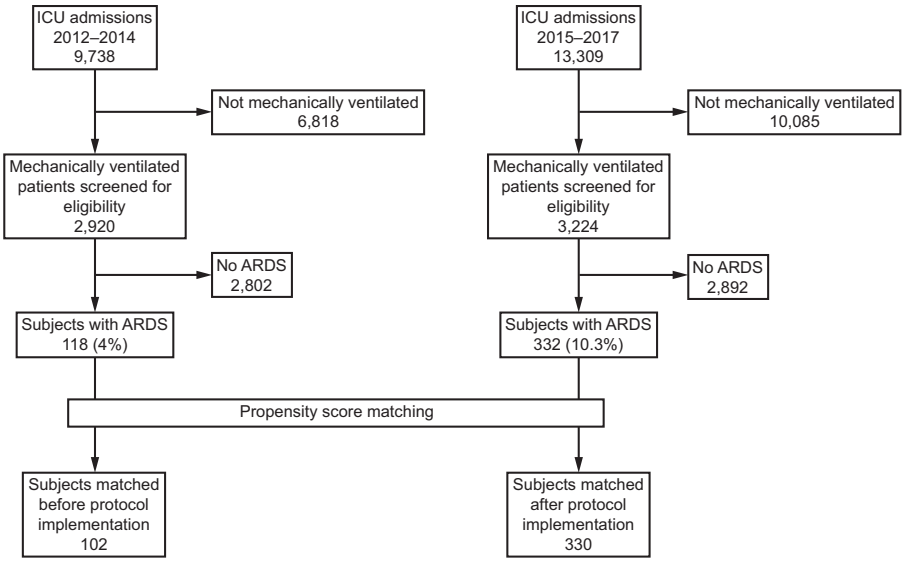

Fig. 1. Flow chart.

shock, P_{aO_2}/F_{IO_2} on day 1, and time from intubation to hospital admission). After propensity score matching, the logistic regression adjustment was used to handle small residual covariate imbalance between the groups.[32] The level of statistical significance was set at $P < .05$ (2-tailed).

Sensitivity Analysis and Subgroup Analysis

Multivariate analyses of variables associated with mortality before and after protocol implementation were performed with and without data imputation. Several models with covariates usually related to mortality were performed to limit confounding. Pre-planned subgroup analysis was performed separately in subjects with moderate to severe ARDS ($P_{aO_2}/F_{IO_2} < 150$).

Results

Subject Characteristics

We identified 450 subjects with ARDS during the study period. The flow diagram of subject selection is shown in Figure 1. A total of 118 subjects (26.2%) were treated before the implementation of the ARDS protocol, and 332 subjects (73.8%) were treated after implementation of the ARDS protocol. Diagnosis of ARDS among the clinical teams improved from 4% to 10.3% ($P < .001$) after implementation of the protocol. Subjects in the protocol group had significantly higher severity of illness at the time of diagnosis of ARDS but had a higher median (IQR) P_{aO_2}/F_{IO_2} of 106 (75–153) versus 128 (88–178) ($P = .02$) and a lower median (IQR) oxygenation index of 15.9 (10.3-26) versus 13.3 (8–22.7) ($P = .034$) on day 1 of ARDS. After the implementation of the ARDS protocol, a lower mean ± SD proportion of subjects were transferred from outside hospitals (76 ± 64.4 vs 173 ± 52.1, $P = .02$). After propensity score matching, both groups had similar baseline characteristics (Table 1). All baseline characteristics were similarly matched in the subgroup of subjects with $P_{aO_2}/F_{IO_2} < 150$ (see the supplementary materials at http://www.rcjournal.com).

Matched Analysis

The percentage of missing values across the 17 variables that were put in matching analysis varied between 0% and 25.6%. The mean airway pressure on day 1 was the most common missing variable, with 32.2% missing in the pre-protocol control group and 23.2% missing in the post implementation of the ARDS protocol group. P_{aO_2}/F_{IO_2} on day 1 was missing in 19.5% of the subjects in the group before ARDS implementation and in 13.3% in after ARDS implementation. Eighteen subjects were excluded from our analysis. Two subjects in the implementation group were excluded because they did not adequately match with the non-implementation group. After matching, covariate balance was improved for all matched variables in subjects. There were 432 subjects in our final analysis. Subjects excluded after matching had a significantly higher P_{aO_2}/F_{IO_2} value, and a greater proportion of subjects had a history of diabetes mellitus, and a significantly oxygenation index on day 1 and severity of illness. In the subgroup of subjects with $P_{aO_2}/F_{IO_2} < 150$, 33 were excluded from our analysis, and 17 subjects in the implementation group were excluded. Subjects excluded after matching had a significantly higher severity of illness, and a higher proportion of

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Table 1. Baseline Characteristic After Propensity Score Matching by ARDS Implementation

	Matched Cohort		*P*
	Before Implementation	After Implementation	
Age, y	55.5 (45.2–66)	58.0 (44.0–67)	.36
Male	53 (52)	178 (53.9)	.73
Body mass index, kg/m^2	31.4 (27.0–39.7)	30.2 (25.2–36.4)	.13
Race			
White	76 (74.5)	241 (73)	.77
Black or African-American	76 (17.6)	75 (22.7)	.28
SOFA score	11 (8–15)	13 (10–16)	.10
Non-pulmonary SOFA score	8 (5–12)	9 (7–12)	.034
APACHE III score	112 (92–139)	117 (98–142)	.23
Charlson comorbidities index	3 (2–6)	4 (2–6)	.62
Comorbidities			
Diabetes mellitus	34 (33.3)	88 (26.7)	.19
Active malignancy	19 (18.6)	68 (2.6)	.66
Liver disease	12 (11.8)	48 (14.5)	.48
Chronic kidney disease	12 (11.8)	48 (14.5)	.48
Heart failure	13 (12.7)	35 (1.6)	.55
Recent surgery (within 3 mo)	1 (1)	16 (4.8)	.09
Chronic lung disease			
COPD	17 (16.7)	44 (13.3)	.40
Idiopathic pulmonary fibrosis	1 (1)	7 (2.1)	.69
Other	12 (11.8)	52 (15.8)	.32
Cause of ARDS			
Pneumonia	80 (78.4)	251 (76.1)	.62
Aspiration	13 (12.7)	64 (19.4)	.13
Non-pulmonary sepsis	11 (1.8)	38 (11.5)	.84
Pancreatitis	5 (4.9)	17 (5.2)	.92
Echocardiography			
Ejection fraction, %	58.3 (55–64)	6.0 (55–65)	.17
Right-ventricular systolic pressure, mm Hg	37.5 (31–47.2)	41.0 (32–5.0)	.25
Septic shock	56 (54.9)	188 (57.1)	.69
Outside hospital transfer	63 (61.8)	173 (52.4)	.10
Time from intubation to hospital admission, d	0 (–3 to 1)	0 (–1 to 3)	.051
P_{aO_2}/F_{IO_2} on day 1	107 (76–165)	128 (87–178)	.08
Oxygenation index on day 1	15.6 (1.0–25.2)	13.4 (8.1–22.8)	.14

Data are presented as median (interquartile range) or *n* (%). *N* = 432 subjects; Before Implementation: *n* = 102 subjects; After Implementation: *n* = 330 subjects.
SOFA = Sequential Organ Failure Assessment
APACHE = Acute Physiology, Age, Chronic Health Evaluation

subjects had a history of chronic kidney disease, diabetes mellitus, aspiration, or septic shock, higher P_{aO_2}/F_{IO_2} and lower oxygenation index on day 1, and shorter time from intubation until hospitalization. Exhibits supporting statements in this paragraph can be found online (see the supplementary materials at http://www.rcjournal.com).

Adherence to the Protocol

A statistically significant decrease was seen in the number of subjects receiving unsafe tidal volume of > 10 mL/kg predicted body weight (14.4% vs 5.8%, $P = .02$). Adherence to safe P_{plat} (≤ 30 cm H_2O) was significantly higher in the implementation arm (76.5% vs 47.4%, $P < .001$) (Table 2). Deviation from recommended PEEP based on the ARDSnet PEEP/F_{IO_2} table was significantly lower after protocol implementation in all subjects and subjects with a P_{aO_2}/F_{IO_2} < 150 (Table 2; see the supplementary materials at http://www.rcjournal.com).

Ventilator Settings, Gas Exchange, and ICU Management

Analysis of cumulative adherence to multiple factors including safe ventilation (tidal volume < 8 mL/kg predicted body weight and $P_{plat} \leq 30$ cm H_2O), PEEP titration

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Table 2. Adherence to Ventilator Settings, Fluid Overload, ICU Interventions, and Other Measures in All Matched Subjects by ARDS Implementation Protocol

	All Matched Cohort		*P*
	Before Implementation	After Implementation	
Average ventilator settings, day 1–3			
Tidal volume, mL/kg PBW			.02
< 8	53 of 90 (58.9)	211 of 308 (68.5)	
8–10	24 of 90 (26.7)	79 of 308 (25.6)	
> 10	13 of 90 (14.4)	18 of 308 (5.8)	
Plateau pressure ≤ 30 cm H_2O	18 of 38 (47.4)	176 of 230 (76.5)	< .001
Driving pressure < 15 cm H_2O*	16 of 38 (42.1)	133 of 230 (57.8)	.07
PEEP discrepancy, cm H_2O†	–7.5 (–1.3 to –4)	–6.3 (–9.3 to –3.3)	.042
ICU interventions and other measures			
Percent of fluid overload, %‡			
Day 1	1.4 (–0.1 to 3.4)	1.3 (–0.3 to 3.4)	.36
Day 2	3.5 (0.8 to 7.9)	2.9 (.4 to 5.9)	.37
Day 3	4.8 (1.1 to 12.2)	4.1 (1.2 to 8.0)	.19
Day 7	6.9 (1.6 to 12.2)	5.4 (1.3 to 1.2)	.21
Day 14	9.1 (3.8 to 17.9)	6.9 (–0.3 to 14.9)	.31
Rescue therapies			
Neuromuscular blocking agents	35 (34.3)	124 (37.6)	.55
Inhaled vasodilators	34 (33.3)	62 (18.8)	.002
Prone positioning	22 (21.6)	27 (8.2)	< .001
Recruitment maneuvers	12 (11.8)	11 (3.3)	< .001
Extracorporeal membrane oxygenation	4 (3.9)	11 (3.3)	.76
High-frequency oscillatory ventilation	1 (1)	2 (0.6)	.56
Sedation	78 (76.5)	251 (76.1)	.93
Analgesia	60 (58.8)	259 (78.5)	< .001
Antipsychotic drugs	39 (38.2)	167 (5.6)	.034
Furosemide	55 (54.5)	153 (46.4)	.15
Acute kidney injury	78 (76.5)	248 (75.2)	.79

Data are presented as *n* (%) or median (interquartile range). $N = 432$ subjects; Before Implementation: $n = 102$ subjects; After Implementation: $n = 330$ subjects.
* Driving Pressure = Plateau Pressure – PEEP.
† PEEP discrepancy is the difference between set PEEP and the ARDS Network PEEP/F_{IO_2} table. Negative values indicate set PEEP was below the PEEP/F_{IO_2} table.
‡ Fluid overload (%) = (fluid intake – total output)/body weight at time of ICU admission × 100.
PBW = predicted body weight

and use of early diuretics, the overall number of subjects treated according to the protocol increased both on day 1 of ARDS and when averaged over the first 72 h of care after the implementation of the protocol. Similar trends were seen when the analysis was limited to subjects with $P_{aO_2}/F_{IO_2} < 150$. There was a significant difference in average tidal volume over the first 3 d of ARDS before and after the implementation of the ARDS protocol (7.65 vs 7.4 mL/kg predicted body weight, $P = .032$) (Table 3). In addition, median (IQR) P_{plat} for the first 3 d was significantly lower in the protocol group (25.5 [IQR 21.7–30] vs 30.5 [IQR 24.2–33] cm H_2O, $P = .01$) (Table 3). PEEP levels for first 3 d were similar in the 2 groups ($P = .20$). Median P_{aO_2}/F_{IO_2} after 24 h of ICU care was significantly higher [155 (IQR 118–204) vs 120 (IQR 96–172), $P < .001$], and median oxygenation index was significantly lower (11.9 [IQR 7.9–17.6] vs 16.5 [IQR 10.3–25.2], $P < .001$) after implementation of the protocol. The incidence of acute kidney injury was similar in both groups (75.2% vs 76.5%, $P = .79$) (Table 2). After the implementation of the protocol, cumulative fluid balance and fluid overload in the first 3 d, at day 7, and at day 14 were similar (Table 2).

After the implementation of the protocol, there was a significant decrease in the use of inhaled vasodilators (18.8% vs 33.3%, $P = .002$), prone ventilation (8.2% vs 21.6%, $P < .001$), and recruitment maneuvers (3.3% vs 11.8%, $P < .001$) (Table 2). The use of analgesic drugs and antipsychotic drugs was significantly increased (78.5% vs 58.8%, $P < .001$, and 50.6% vs 38.2%, $P = .031$, respectively) after the implementation of the protocol. These differences remained significant in subjects with $P_{aO_2}/F_{IO_2} < 150$ on day 1. There was no difference in the use of sedative agents and diuretics between the 2 groups ($P = .93$ and $P = .15$). Exhibits supporting statements in this subsection can be found online (see the supplementary materials at http://www.rcjournal.com).

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Table 3. Ventilator Settings and Gas Exchange of All Matched Subjects by ARDS Implementation Protocol

	Matched Cohort		*P*
	Before Implementation	After Implementation	
Average ventilator settings, day 1–3			
F_{IO_2}	0.75 (0.6–0.90)	0.63 (0.5–0.79)	< .001
Tidal volume, mL/kg PBW	7.65 (7.1–8.5)	7.4 (6.7–8.4)	.032
PEEP, cm H_2O	10 (8–14.0)	10 (8–13.3)	.20
Plateau pressure, cm H_2O	30.5 (24.2–33)	25.5 (21.7–30)	.01
Peak airway pressure, cm H_2O	30.7 (27.0–35.0)	29.7 (25.5–34.3)	.08
Mean airway pressure, cm H_2O	18.7 (15.8–22.8)	17.0 (14.0–2.3)	.002
Minute ventilation, L/min	11.8 (1.1–14.2)	10.8 (8.8–12.5)	< .001
Driving pressure, cm H_2O*	15 (13.0–17.4)	14 (11.3–17.9)	.21
Average gas exchange, day 1–3			
P_{aO_2}/F_{IO_2}	120 (96–172)	155 (118–204)	< .001
Oxygenation index	16.5 (1.3–25.2)	11.9 (7.9–17.6)	< .001
P_{aCO_2}, mm Hg	42 (37.5–47.3)	42 (36.3–48.2)	.84
pH	7.34 (7.29–7.40)	7.34 (7.29–7.39)	.64

Data are presented as median (interquartile range). $N = 432$ subjects; Before Implementation: $n = 102$ subjects; After Implementation: $n = 330$ subjects.
* Driving pressure = Plateau pressure – PEEP.
PBW = predicted body weight

Table 4. Outcomes Analysis in All Matched Subjects

	All Matched Subjects							
	Before Implementation		After Implementation		Crude Odds Ratio (95% CI)*	*P*	Adjusted Odds Ratio (95% CI)†	*P*
Mortality								
28-d	55	(53.9)	138	(41.8)	0.61 (0.39–0.96)	.031	0.47 (0.28–0.78)	.004
90-d	63	(61.8)	159	(48.2)	0.58 (0.37–0.91)	.02	0.45 (0.27–0.76)	.003
Length of ICU stay, d	13.5	(8–21)	12.0	(7–20)		.21		
Length of hospital stay, d	19.5	(10–26.8)	17.0	(12–27.0)		.95		
Ventilator-free days, d	0	(0–8)	0	(0–17)		.002		
Discharge types								
Home	10	(9.8)	64	(19.5)		.02		
Other discharge types	33	(32.4)	122	(37.1)				
Died	59	(57.8)	143	(43.5)				

Data are presented as *n* (%) or median (interquartile range).
* Univariable logistic regression of 50 imputed data sets.
† Multivariable logistic regression of 50 imputed data sets (adjustment for age, APACHE III score, Charlson comorbidity index, septic shock, P_{aO_2}/F_{IO_2} on day 1, and time from intubation to hospital admission).

Outcomes

Mortality at day 28 improved after the implementation of the ARDS protocol (41.8% vs 53.9%, adjusted odds ratio 0.47 [95% CI 0.28–0.78], $P = .004$). Mortality at day 90 was similarly significantly lower (48.2% vs 61.8%, adjusted odds ratio 0.45 [95% CI 0.27–0.76], $P = .003$) (Table 4). The mortality reduction at 28 d and 90 d was much more pronounced in subjects with $P_{aO_2}/F_{IO_2} < 150$, with adjusted odds ratios of 0.39 (95% CI 0.19–0.80, $P = .01$) and 0.31 (95% CI 0.15–0.64, $P = .002$), respectively (Table 5). After implementation of the protocol, the median (IQR) ventilator-free days increased (0 [0–17] vs 0 [0–8], $P = .002$) and more subjects were discharged home (19.5% vs 9.8%, $P = .02$). However, there was no difference in length of ICU or hospital stay between the 2 groups (Table 4).

Sensitivity Analysis and Subgroup Analysis

The 28-d and 90-d multivariable logistic regression of non-imputed data showed that the implementation of the protocol had a significant reduction in mortality after adjustment for confounding factors including age, presence of septic shock, APACHE III score, Charlson comorbidity

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Table 5. Outcomes Analysis in Matched Subjects With $P_{aO_2}/F_{IO_2} < 150$

Outcomes	Matched Subjects With $P_{aO_2}/F_{IO_2} < 150$							
	Before Implementation		After Implementation		Crude Odds Ratio (95% CI)*	*P*	Adjusted Odds Ratio (95% CI)†	*P*
Mortality								
28-d	30	(54.5)	61	(37.9)	0.51 (0.27–0.95)	.031	0.39 (0.19–0.80)	.01
90-d	36	(65.5)	71	(44.1)	0.42 (0.22–0.79)	.01	0.31 (0.15–0.64)	.002
Length of ICU stay, d	16	(10–24)	13	(8–21)		.13		
Length of hospital stay, d	20	(14.5–31)	20	(13.0–29)		.66		
Ventilator-free days, d	0	(0–6)	0	(0–17)		.01		
Discharge types								
Home	5	(9.1)	34	(21.1)		.034		
Other discharge types	17	(30.9)	60	(37.3)				
Died	33	(60)	67	(41.6)				

Data are presented as *n* (%) or median (interquartile range).

* Univariable logistic regression of 50 imputed data sets.

† Multivariable logistic regression of 50 imputed data sets (adjustment for age, APACHE III score, Charlson comorbidity index, septic shock, P_{aO_2}/F_{IO_2} on day 1, and time from intubation to hospital admission).

index, time from intubation to hospital admission, and P_{aO_2}/F_{IO_2} on day 1. The adjusted odds ratios for 28-d and 90-d mortality in the implementation group were 0.49 (95% CI 0.28–0.85, $P = .01$) and 0.44 (95% CI 0.25–0.75, $P = .003$), respectively. The 28-d and 90-d mortality benefits were also significant in subjects with $P_{aO_2}/F_{IO_2} < 150$ (see the supplementary materials at http://www.rcjournal.com).

Discussion

In this observational before-and-after study, the use of a multi-domain ARDS protocol preceded by a structured education curriculum was associated with 12% absolute reduction in mortality and increased discharge home by 10%. Implementation of the protocol improved clinician recognition of ARDS and improved the ICU team's attentiveness to unsafe tidal volumes and airway pressures. Similar to other recent studies, our analysis confirms that the use of lung-protective ventilation is not ubiquitous in ICU practice and significant practice variations exist.[1,33] The implementation of our protocol resulted in a detectable decrease in the median tidal volume and exposure to unsafe ventilation. Implementation of the protocol was also associated with better adherence to the ARDSnet PEEP/F_{IO_2} tables, which facilitates more generalizable PEEP titration. Application of the PEEP/F_{IO_2} tables according to the ARDS protocol was achieved through collaboration with the respiratory therapy department. Its increased utilization attests to the successful implementation of our protocol.[34]

After implementation of the protocol, the P_{plat} for the first 72 h of ICU care was much lower and adherence to PEEP titration was much higher. Driving pressures were detectably lower in subjects with moderate-to-severe ARDS on the first day of diagnosis. In this group, the improvement in their driving pressure coincided with significantly higher P_{aO_2}/F_{IO_2} on day 2 and day 3, improvement in their ventilator-free days, and improvement in survival and discharge home. These findings are in line with the recent study by Amato et al,[35] who reported that lower driving pressures are associated with better outcomes in subjects with ARDS.

Use of optimal ventilator settings remains low, and a number of barriers at system, institutional, and clinician levels have been identified in previous studies.[14,16] After implementation of our protocol, we not only improved adherence to recommended approaches to ARDS management, but, perhaps more importantly, we were able to decrease the numbers of outliers who were receiving unsafe settings. Despite encouragement toward early use of prone ventilation, we saw that its use decreased after the implementation of the protocol. The marked improvement in the day 2 P_{aO_2}/F_{IO_2} might have been the major reason for this change. Guerin et al[12] reported that clinician perception that the hypoxemia is not severe enough or is improving is the most common reason for not implementing prone ventilation. Interestingly, the use of inhaled vasodilators and recruitment maneuvers also decreased significantly after the institution of our protocol. This is a compelling argument supporting the theory that early optimization of mechanical ventilation with minimization of ongoing ventilator-induced lung injury can potentially decrease the need for adjunctive and rescue therapies.

We acknowledge that our study has several limitations, namely the single-center before-and-after design, which cannot account for coexistent temporal trends. Though the data were collected retrospectively, all patients were actively screened for ARDS prospectively. We used

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propensity score adjustment in an attempt to control for any potential confounders. The baseline similarities in our cohort resulted in a minimal loss of subjects after matching. Subject characteristics, utilization of therapies, and baseline compliance with different recommendations for ARDS management were comparable to previously published data.[1] Although every effort was made to account for missing data, due to the retrospective nature of the study, some remained missing. We applied multiple imputations for these missing variables and used the results to perform propensity matching and sensitivity analysis. Multiple statistical models with different covariates and subgroup analyses reached the same conclusion. Likewise, a drawback of before-and-after studies is that potential difference in practice over time might influence outcomes. However, the very nature of our question is exploring the aforementioned variation. Our scientific endeavor was to observe the impact of protocol implementation on physician behavior and its clinical impact on patient outcomes over time. We also looked at both 28-d and 90-d mortality as our outcome variables of interest, which provides a more robust assessment of the overall outcomes for these subjects. Assuming the internal consistency of our data, the improved outcomes subsequent to the implementation of our protocol are reflective of the additive effect of sequential therapies based on physiological models that have been consistently elaborated in published literature.

Other literature describing protocolized care in ARDS has focused on subjects on the severe end of the disease spectrum, showing benefits in terms of increasing use of adjunctive prone positioning and aiding in decision-making for patients with refractory hypoxemia.[36,37] To our knowledge, this is the first study that has investigated the protocolized implementation of evidence-based management with combined provider education to improve the utilization of different management domains and strategies for all patients with ARDS. Our results indicate that the implementation of optimal therapies with a strong evidence base in a protocolized, sequential manner can have a significant impact on patient survival and other outcomes in ARDS. The use of lung-protective ventilation strategies in conjunction with ensuring patient synchrony and conservative fluid strategies ensured that we did not have to escalate to adjunctive or rescue therapies in a number of our subjects. The mortality rate in our study was improved because of an individual piece, but the bundle of ARDS treatments make the difference.

Conclusions

A robust, multi-domain, ARDS management protocol, paired with provider education, improved the adherence to evidence-based management in subjects with ARDS. Implementation of such a protocol was associated with improved survival, increased the rate of discharge home, and decreased the utilization of adjunctive and rescue interventions.

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