Epidemiology, Mechanical Power, and 3-Year Outcomes in Acute Respiratory Distress Syndrome Patients Using Standardized Screening

An Observational Cohort Study

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Abstract

Rationale: Limited data on the epidemiology of acute respiratory distress syndrome (ARDS) using a standardized screening program exist.

Objectives: To describe the population-based incidence of hypoxemic respiratory failure and ARDS using a prospective standardized screening protocol; and to describe the mechanical ventilation practice and the mechanical power and examine their association with 28-day and 3-year survival outcomes.

Methods: A prospective standardized screening program for ARDS, as a quality improvement initiative, was initiated at four adult intensive care units over a 27-month period. An ancillary analysis of this observational cohort was performed. Patients requiring mechanical ventilation for ⩾24 hours underwent prospective and consecutive screening using standardized ventilator settings. Patient physiological data and outcomes were collected prospectively through an electronic clinical-information system and retrospectively analyzed to apply Berlin criteria.

Results: Screened were 7,944 patients, among which 986 (12.4%) had hypoxemic respiratory failure (arterial oxygen tension to inspired fraction of oxygen ratio ⩽300), and 731 (9.2%) met criteria for ARDS. Age-adjusted incidence of hypoxemic respiratory failure and ARDS were 37.7 and 27.6 cases per 100,000 person-years, respectively. Patients sustaining the diagnosis of ARDS had a hospital mortality of 26.5% for mild, 31.8% for moderate, and 60.0% for severe ARDS and a 3-year mortality of 43.5% for mild, 46.9% for moderate, and 71.1% for severe ARDS. Mechanical power >22 J/min was associated with increased 28-day hospital and 3-year mortality. Determinants of mechanical power associated with lower 28-day hospital and 3-year survival included plateau pressure >30 cm H_2O and driving pressure >15 cm H_2O, but not tidal volumes >8 ml/kg of predicted body weight.

Conclusions: Using standardized screening, a large proportion of patients with hypoxemic respiratory failure met criteria for ARDS. Increasing ARDS severity was associated with increased 28-day hospital and 3-year mortality. Increased mechanical power was associated with increased mortality. Potentially modifiable determinants of mechanical power associated with lower survival included plateau pressure and driving pressure.

Keywords: respiratory distress syndrome; adult; mechanical ventilation

(Received in original form December 21, 2018; accepted in final form June 26, 2019)

Supported by Alberta Critical Care Strategic Clinical Network (K.K.S.P.) and Calgary Chief Medical Office and Medical Affairs (K.K.S.P.) to conduct this study.

Author Contributions: Study design and literature search: K.K.S.P., K.Z., C.L., and C.J.D. Data collection, interpretation, and analysis: K.K.S.P., K.Z., A. Soo, A. Sutton, M.Z., L.D., A.F., D.J.N., K.M.F., H.T.S., and C.J.D. Manuscript writing, revisions, and drafting of figures: K.K.S.P., A. Soo, D.J.N., K.M.F., H.T.S., and C.J.D.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Ann Am Thorac Soc Vol 16, No 10, pp 1263–1272, Oct 2019

DOI: 10.1513/AnnalsATS.201812-910OC
Internet address: www.atsjournals.org

Acute respiratory distress syndrome (ARDS) is an inflammatory condition of the lungs. It is caused by either direct or indirect injury, and results in a clinical syndrome of hypoxemia, bilateral lung infiltrates, and increased vascular permeability (1). ARDS is associated with significant morbidity and mortality, whereby severe ARDS has an observed mortality rate of more than 40% (2–5). The most recent definition of ARDS (Berlin) includes key features that represent the syndrome of ARDS and can prognosticate mortality and ventilator-free days based on the severity of hypoxemia (3, 6).

Mechanical ventilation practice can also influence prognosis in ARDS. This is likely through its effect on secondary iatrogenic ventilator-induced lung injury (7–9). For example, application of excess tidal volume or a large driving pressure has been associated with poor outcomes (7, 9). Mechanical power is a recently described method to estimate the amount of energy (J/min) being transferred to the patient from mechanical ventilation, with its key determinants being respiratory rate, driving pressure, peak pressure, and tidal volume (8). Moreover, mechanical ventilation practice, in particular the association between mechanical power and survival outcomes, has not been well described in patients with hypoxemic respiratory failure and ARDS.

Despite strong evidence supporting the use of lung-protective ventilation, mechanical ventilation practice can vary significantly in patients with ARDS, perhaps highlighting underdiagnosis and poor knowledge translation (2). Formalized screening protocols using standardized ventilator settings and patient conditions for the purpose of surveillance and diagnosis of ARDS are not routine practice (2, 10–13). Lack of standardized screening may lead to underdiagnosis or misclassification of severity for several reasons. First, there is a nonlinear relationship between fraction of inspired oxygen ($F_{I_{O_2}}$) and arterial oxygen tension to inspired fraction of oxygen ratio (PF ratio) and therefore the applied $F_{I_{O_2}}$ can influence the PF ratio at the time of diagnosis (14–16), potentially leading to misclassification of the severity of ARDS. Second, screening for ARDS using standardized settings, such as timing, positive end-expiratory pressure (PEEP), and $F_{I_{O_2}}$, improves the accuracy and durability of a diagnosis of ARDS (17–20). Third, appropriate recognition of ARDS may lead to modifications in ventilator management because underrecognition of ARDS is more likely to be treated with higher tidal volumes and lower PEEP and reduced use of ancillary therapies (2). Finally, using single arterial blood gas (ABG) results to make the diagnosis of ARDS, which may be conducted during times of transient instability, such as mucous plugging, may lead to overdiagnosis, misclassification, or overestimation of the severity ARDS (18, 20). To date, the incidence, detailed assessment of mechanical ventilation practice, and long-term outcomes of hypoxemic respiratory failure and Berlin definition ARDS using a standardized screening protocol have not been described.

We present an observational cohort of patients with hypoxemic respiratory failure and ARDS (Berlin definition) diagnosed using a prospective standardized ARDS screening protocol. The primary objective of this study was to describe the population-based incidence of hypoxemic respiratory failure and ARDS using a prospective standardized screening protocol. The secondary objectives of this study were to describe mechanical ventilation practice and the mechanical power and its association with 28-day hospital and 3-year survival outcomes.

Methods

Study Design

Recruitment of patients was directed by a quality improvement initiative aimed at standardizing the identification of patients with ARDS. All four intensive care units (ICUs) at three hospitals within the boundaries of Calgary, Alberta, Canada, participated in this study. Participants were prospectively and consecutively enrolled over a period of 27 months (October 2010 to December 2012). Patients were included if they were admitted to ICU, invasively ventilated for 24 hours or more, and had a PF ratio of $\leq$300 mm Hg (adjusted to sea level) on any ABG. Screening consisted of an ABG on standardized ventilator settings being conducted along with a chest radiograph being performed. Before conducting the ABG, the $F_{I_{O_2}}$ was maintained at 1.0 for 30 minutes (to ensure a comparable PF ratio between all patients), a standardized PEEP of $\geq$5 cm H_2O was applied, and the patients were at clinical steady state (not desaturating acutely).

Screening was performed by respiratory therapists and protocol compliance was supervised and audited by respiratory therapist supervisors. Validated patient data (by nursing and respiratory therapists) and outcomes were prospectively collected in electronic clinical information systems (TRACER and DIMR) with data manually audited (DK) for accuracy and completion, as previously described (21). Missing patient demographics were retrospectively abstracted by chart reviews as required. Three-year mortality was abstracted in June 2017 from the Alberta Vital Statistics registry by providing a list of patients with their unique lifetime identifier/personal health number to DIMR (Alberta Health Services, Alberta, Canada) who receives data periodically from Alberta Vital Statistics. At the time of data linkage, data were available until December 31, 2015, which provided full 3-year follow-up for all patients. Berlin criteria for ARDS (instead of the previous American-European Consensus Conference [AECC] definition) were applied *post hoc* for the analysis of mechanical ventilation practice (3, 6). Chest radiographs were retrospectively reviewed by two independent reviewers (K.K.S.P. and C.J.D.) using the Berlin definition radiograph guideline (6). *Post hoc* analysis included calculation of driving pressure and mechanical power (*see* below for details). The study is reported according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement guidelines for observational cohort studies (22).

Outcomes

The primary outcome was the incidence of hypoxemic respiratory failure and ARDS using a standardized screening protocol. The secondary outcomes were survival (28-d hospital and 3-yr), 28-day ventilator-free days, 28-day ICU-free days, and ICU and hospital length of stay. Ventilator-free days were calculated as previously described (23). ICU-free days (a composite of mortality and ICU length of stay) were calculated as 28 days minus number of calendar days in ICU; for patients who died in ICU within 28 days or patients who stayed longer than 28 days in ICU, ICU-free days were set to 0.

Definitions of ARDS and Calculation of Mechanical Power

"Hypoxemic respiratory failure" were patients with a standardized ABG

demonstrating a PF ratio ⩽300 mm Hg. ARDS was defined using the Berlin definition and retrospectively applied to the study cohort (3). Chest radiographs were retrospectively reviewed by two independent reviewers (K.K.S.P. and C.J.D.) using the Berlin definition radiograph guideline (6). ARDS severity was categorized into mild (200 < PF ratio ⩽300 mm Hg), moderate (100 < PF ratio ⩽200 mm Hg), or severe (PF ratio ⩽100 mm Hg).

"Non-ARDS" hypoxemic respiratory failure were patients with hypoxemic respiratory failure but not meeting ARDS criteria. "Sustained ARDS" were patients who maintained PF ratio criteria for ARDS on a second nonstandardized ABG conducted 12–36 hours later (*see* Figure E1 in the online supplement). "Driving pressure" was calculated as plateau pressure (P_{plat}) − PEEP. Mechanical power was calculated using the formula $Power = 0.098 \cdot RR \cdot \Delta V \cdot (Ppeak - 0.5 \cdot \text{Driving Pressure})$ as previously described (8). For analysis, lung-protective ventilation cutoffs of 8 ml/kg of predicted body weight (PBW) and P_{plat} ⩽30 cm H_2O were used, as previously reported (2). The thresholds for driving pressure and mechanical power were determined through receiver operating characteristic analysis using logistic regression and Youden J statistic, which maximizes sensitivity plus specificity (24).

Incidence

Patients were defined as Calgary residents using their postal code of primary residence. The closest tertiary ICU outside of Calgary is 298 km away (Edmonton) and the closest regional ICU is 149 km away (Red Deer) making it highly unlikely a Calgary resident would seek care in an external jurisdiction. Population data for adults aged 19 and older within the Calgary area in 2011–2012 (2-yr period) were derived from Province of Alberta Provincial Registry data using the Alberta Health Population Projections. Patients with an unknown postal code were assumed to be non-Calgary residents and excluded. The Calgary area population for adults aged 19 and older during 2011 and 2012 were 1,080,231 and 1,117,213, respectively (mean, 1,098,722). Age-adjustment was performed with the general population within Canada using the standardized population from 2011 Government of Canada national census data (25).

Statistical Analyses

Patient characteristics and outcomes are described using frequency with percentage, or median with interquartile range as appropriate. Patient characteristics and outcomes were compared between groups using chi-square tests, Wilcoxon rank sum tests, or Kruskal-Wallis tests as appropriate. Time to hospital and 3-year mortality starting from first standardized ABG was evaluated using Kaplan-Meier survival curves and compared between groups using log-rank tests. For 28-day hospital mortality, patients discharged home before Day 28 were censored at time of hospital discharge. For the exploratory analyses of the association between ventilator-free days and length of stay outcomes by determinants of mechanical power, *P* values were adjusted for multiple comparisons using a Bonferroni correction multiplying *P* values by 20 for $n = 20$ comparisons. A two-sided *P* value <0.05 was considered statistically significant. Analyses were conducted using the statistical software R version 3.5.1 (26).

Ethics

This study was approved by the Conjoint Health Research Ethics Board in Calgary, Alberta (REB approval 17–0941).

Results

Patient Recruitment and ARDS Standardized Screening

During the 27-month study period, 7,944 patients admitted to one of the four ICUs were screened for eligibility (*see* Figure E1). Of this group, 1,250 patients were invasively ventilated for >24 hours and had a PF ratio ⩽300 mm Hg (on a nonstandardized ABG) and met criteria for a standardized ABG. Using a standardized ABG, 986 patients of 7,944 total patients admitted (12.4%) were defined as hypoxemic respiratory failure (PF ratio ⩽300 mm Hg), and 264 patients were excluded because of a PF ratio >300 mm Hg. Of the 986 patients, 731 met Berlin definition ARDS criteria (9.2% of 7,944 patient cohort). The remaining 255 patients with a PF ratio ⩽300 mm Hg not meeting ARDS criteria were defined as non-ARDS hypoxemic respiratory failure. Of the 731 patients with ARDS, 633 patients (86.6%) had sustained ARDS (PF ratio ⩽300 mg Hg on a repeat ABG 12–36 h later).

Incidence of Hypoxemic Respiratory Failure and ARDS with Standardized Screening

Age-adjusted incidence of hypoxemic respiratory failure and ARDS were 37.7 and 27.6 cases per 100,000 person-years, respectively (Table 1). The crude incidence of ARDS was higher in men than in women (33.9 vs. 21.4 cases per 100,000 person-years, respectively). The crude incidence of ARDS increased by age decile with a peak incidence in the 70–79 years age-group. The incidence of hypoxemic respiratory failure and ARDS per ICU bed per 4-week period was 0.53 and 0.39, respectively. Comparison of incidence during fall and winter versus spring and summer did not suggest seasonal differences (*see* Table E1).

Demographics and Physiology of Patients with Hypoxemic Respiratory Failure and ARDS

Univariate analysis suggests a higher prevalence of preexisting coronary artery disease and heart failure in patients with non-ARDS hypoxemic respiratory failure versus ARDS (*see* Table E2). Patients with ARDS had higher rates of pneumonia, sepsis, abdominal surgery, and immunosuppression than patients with non-ARDS hypoxemic respiratory failure (*see* Table E2).

Sequential organ failure assessment scores at presentation were slightly higher for patients with non-ARDS hypoxemic respiratory failure (*see* Table E2); however, admission Acute Physiology, Age, and Chronic Health Evaluation II scores were similar between groups. The increase in sequential organ failure assessment scores for patients with non-ARDS hypoxemic respiratory failure was primarily attributable to the renal and cardiac sequential organ failure assessment components. A larger proportion of patients with non-ARDS hypoxemic respiratory failure required inotropes, whereas patients with ARDS had a higher cumulative fluid balance (*see* Table E3). Both ARDS and non-ARDS hypoxemic respiratory failure had similar PF ratios; however, patients with ARDS were more hypercarbic on diagnosis. Patients with ARDS had more severe hypoxemia, hypercarbia, and acidosis on their worst ABG during their ICU stay (*see* Table E3).

There were 633 patients that met criteria for sustained ARDS with 31.6% having mild ($n = 200$), 54.2% having

Table 1. Crude and age-adjusted incidence of HRF and ARDS

Variable	HRF (*n* = 986)	ARDS (*n* = 731)	Non-ARDS HRF (*n* = 255)
Total Calgary cases >19 yr, *n**	702 (71.2)	515 (70.4)	187 (73.3)
Crude incidence (cases/100,000 person-years)	32.0	23.4	8.5
Mild ARDS		9.7	
Moderate ARDS		6.8	
Severe ARDS		7.0	
Age-adjusted incidence (cases/100,000 person-years)	37.7	27.6	10.0
Males	46.8	33.9	13.0
Females	28.5	21.4	7.1
Mild ARDS		11.3	
Moderate ARDS		8.0	
Severe ARDS		8.2	
Crude incidence by age decile			
20–29	5.2	3.6	1.6
30–39	11.1	7.3	3.8
40–49	20.3	15.6	4.7
50–59	41.4	30.5	10.8
60–69	80.3	61.9	18.4
70–79	104.1	72.8	31.3
80–89	88.0	60.8	27.2
90 and above	16.9	16.9	0.0
Incidence per ICU bed (per 4-wk period)†	0.53	0.39	0.14
Annual cases in Canada >19 yr	9,974	7,315	2,658
Annual deaths in Canada >19 yr	4,109	2,912	1,194
Estimated annual ICU days‡	92,352	73,636	17,910
Estimated annual hospital days§	210,463	161,131	51,165

Definition of abbreviations: ARDS = acute respiratory distress syndrome; HRF = hypoxemic respiratory failure; ICU = intensive care unit.
Percentage of total patients per category listed in parentheses.
*Calgary residents determined using postal code or registered address.
†Includes all patients diagnosed with HRF or ARDS and does not exclude patients outside of Calgary zone.
‡Estimated annual ICU days estimated using median ICU length of stay and age-adjusted incidence.
§Estimated annual hospital days estimated using median hospital length of stay and age-adjusted incidence.

moderate ($n = 343$), and 14.2% having severe ($n = 90$) ARDS (Table 2). Patients with moderate or severe ARDS had a lower PBW (Table 2). The prevalence of comorbidities and risk factors for ARDS did not change with severity of ARDS (*see* Table E4). Severity of ARDS was associated with higher severity of illness scoring both on admission and during the ICU stay (*see* Table E4) and more vasoactive use (*see* Table E5). Increasing severity of ARDS was associated with higher proportions of patients receiving continuous renal-replacement therapy (*see* Table E5).

Mechanical Ventilation Practice in Patients with Hypoxemic Respiratory Failure and ARDS

Patients with ARDS, in comparison with patients with non-ARDS hypoxemic respiratory failure, had longer duration of mechanical ventilation, higher respiratory rates and minute ventilation, higher peak and P_{plat}, higher mean airway pressures, higher PEEP, and slightly lower median tidal volumes (*see* Table E3 and Figure E3). Patients with ARDS had significantly higher mechanical power in comparison with non-ARDS hypoxemic respiratory failure, despite having a similar driving pressure (*see* Table E3).

During mechanical ventilation, increasing severity of ARDS was associated with higher median respiratory rates, peak pressures, P_{plat}, mean airway pressures, and PEEPs (Table 2; *see* Figure E4). Mechanical power and driving pressure increased with severity of ARDS (Table 2). There was also an association between severity of ARDS and the use of inhaled vasodilators, recruitment maneuvers, and neuromuscular blockade (*see* Table E5).

Outcomes in Patients with Hypoxemic Respiratory Failure and ARDS

Patients with ARDS had similar ventilator-free days when compared with patients with non-ARDS hypoxemic respiratory failure (*see* Table E3); however, ICU and hospital length of stay was longer for patients with ARDS. Patients with non-ARDS hypoxemic respiratory failure versus patients with ARDS had higher ICU and hospital mortality; however, mortality was similar at 3 years (Figure 1; *see* Table E3).

Severity of sustained ARDS was associated with lower ventilator-free days; lower ICU-free days; and higher ICU, hospital, and 3-year mortality (Table 2; *see* Figure E3). Patients with ARDS, when stratified by their first standardized ABG with a PF ⩽300 mm Hg, had a statistically significant reduction in 28-day hospital and 3-year survival with increasing severity (Figure 1). Stratification by worst ABG or follow-up sustained ABG was not able to differentiate 28-day hospital or 3-year survival outcomes between mild and moderate ARDS (*see* Figure E2). Among those patients with sustained ARDS who survived to hospital discharge, 77% (321 of 417) survived to 3 years.

Association of Mechanical Power with Outcomes

The thresholds for mechanical power and driving pressure are presented in Table E6. The threshold of 22 J/min for mechanical power was used based on the more proximal outcome of 28-day survival. Mechanical power of >22 J/min was associated with lower ventilator-free days and hospital survival at 28 days and survival at 3 years in patients with sustained ARDS (Figure 2, Table 3; *see* Figure E5).

For determinants of mechanical power, a P_{plat} >30 cm H_2O and a median driving pressure >15 cm H_2O was associated with lower hospital survival at 28 days and survival at 3 years (Figure 2; *see* Figure E5). Tidal volume >8 ml/kg of PBW was not associated with any change in mortality (Figure 2; *see* Figure E5). P_{plat} >30 cm H_2O and driving pressure >15 cm H_2O were all associated with lower ventilator-free days (Table 3).

Discussion

In this observational study examining the incidence and outcomes of patients with

Table 2. Baseline demographics, physiology, and outcomes of patients with ARDS by severity

Variable	All ARDS (*n* = 633)	Mild (*n* = 200)	Moderate (*n* = 343)	Severe (*n* = 90)
Selected baseline characteristics				
Age, median (IQR)	60 (49–69)	60 (50–68)	60 (49–69)	59 (50–69)
Sex, female	218 (34.5)	62 (31.0)	117 (34.2)	39 (43.3)
Predicted body weight, kg	66 (57–75)	69 (57–75)	66 (57–74)	62 (56–71)
SOFA, at admission (total)	9 (7–12)	9 (7–11)	9 (6–11)	11 (8–14)
SOFA, worst during ICU stay	11 (8–14)	10 (8–12)	11 (8–14)	14 (10–16)
ABG, first ARDS*				
PF ratio	178 (96–242)	236 (167–267)	167 (106–228)	80 (65–97)
pH	7.37 (7.30–7.43)	7.40 (7.34–7.45)	7.37 (7.30–7.42)	7.32 (7.25–7.39)
Pa_{CO_2}	40 (35–46)	39 (34–43)	40 (36–48)	42 (35–51)
Pa_{O_2}	178 (96–242)	236 (167–267)	167 (106–228)	80 (65–97)
Sa_{O_2}	96 (95–97)	97 (96–97)	96 (95–97)	93 (91–95)
Mechanical ventilation practice				
Respiratory rate	22 (19–25)	20 (18–24)	22 (19–26)	23 (20–28)
Minute ventilation, L/min	11 (10–13)	11 (10–13)	11 (10–13)	12 (10–13)
Peak pressure, cm H_2O	26 (23–29)	24 (21–27)	26 (23–29)	30 (26–33)
Plateau pressure, cm H_2O	26 (23–29)	24 (21–28)	26 (24–29)	28 (26–31)
Mean airway pressure, cm H_2O	15 (13–17)	14 (12–15)	15 (13–17)	17 (15–20)
Driving pressure	15 (12–18)	15 (12–17)	14 (12–17)	16 (14–19)
PEEP, cm H_2O	10 (8–12)	10 (8–10)	10 (10–12)	10 (10–12)
Tidal volume, ml/kg PBW	8.1 (7.4–9.1)	8.2 (7.4–9.1)	8.0 (7.4–9.1)	8.4 (7.3–9.0)
Mechanical power	25 (19–32)	22 (18–30)	26 (20–32)	27 (21–33)
Outcomes				
Duration of mechanical ventilation, d	9 (5–15)	8 (5–13)	9 (6–16)	10 (4–16)
Ventilator-free days	14 (0–21)	18 (0–23)	14 (0–21)	0 (0–12)
ICU-free days	9 (0–18)	14 (2–20)	10 (0–18)	0 (0–6)
ICU length of stay, d	11.7 (6.2–18.4)	10.3 (6.0–15.4)	12.5 (6.8–19.6)	10.3 (3.7–20.1)
ICU mortality	171 (27.0)	39 (19.5)	82 (23.9)	50 (55.6)
Hospital length of stay, d	24.6 (14.2–44.2)	24.9 (15.5–44.3)	25.3 (16.0–44.9)	15.2 (7.1–37.0)
Hospital mortality	216 (34.1)	53 (26.5)	109 (31.8)	54 (60.0)
28-d hospital mortality	189 (29.9)	47 (23.5)	93 (27.1)	49 (54.4)
3-yr mortality	312 (49.3)	87 (43.5)	161 (46.9)	64 (71.1)

Definition of abbreviations: ABG = arterial blood gas; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range; Pa_{CO_2} = partial pressure of arterial carbon dioxide; Pa_{O_2} = partial pressure of arterial oxygen; PBW = predicted body weight; PEEP = positive end-expiratory pressure; PF = fraction of inspired oxygen and arterial oxygen tension to inspired fraction of oxygen ratio; Sa_{O_2} = arterial oxygen saturation percentage; SOFA = sequential organ failure assessment.

All categorical data presented as number (percentage) and continuous data presented as median (interquartile range).

*ABG conducted on F_{IO_2} 1.0.

hypoxemic respiratory failure and ARDS prospectively identified using a standardized screening protocol, we observed that both hypoxemic respiratory failure and ARDS had a significant incidence among ICU admissions (12.4%), the incidence increased with decile of age, and the diagnosis was associated with significant mortality. Use of standardized screening identified patients with hypoxemic respiratory failure, of which a high proportion met ARDS criteria. Patients with ARDS and non-ARDS hypoxemic respiratory failure had similar long-term survival. Increasing severity of ARDS was associated with a lower probability of survival. Increasing severity of ARDS was also associated with a higher mechanical power. Mechanical power and its determinants P_{plat} and driving pressures were associated with a lower probability of survival at 28 days and 3 years; however, lower tidal volume was not associated with increased survival.

By using standardized screening for ARDS, we are able to present a relatively unbiased assessment of hypoxemic respiratory failure and ARDS incidence and 3-year outcomes. Standardized screening is also associated with durability of diagnosis, because 97.2% of patients (633 of 651 patients with a repeat ABG) (*see* Figure E1) who met ARDS criteria on their initial ABG continue to meet ARDS criteria on a follow-up ABG 12–36 hours later. Previous studies using standardized ventilator settings led to a significant proportion of patients being reclassified from moderate or severe ARDS to resolved or a milder grade of ARDS (18, 19, 27). These studies were limited by small numbers of patients and the use of the older AECC definition for ARDS. A recent ancillary analysis of the LUNG SAFE cohort (which did not use standardized screening) demonstrated 24% of patients were reclassified on Day 2 as resolved or a milder grade of ARDS (28). Standardized screening minimizes the bias of including patients receiving ABGs during periods of temporary instability, for example misclassifying a patient in a more severe category because of an acute desaturation from mucous plugging that would otherwise quickly resolve. Misclassifying patients as more severe could lead to underestimation of the true morbidity and mortality, in addition to having implications for the enrollment of patients into clinical trials (20).

Mechanical ventilation practice can influence ventilator-induced lung injury and outcome. By using a standardized screening protocol along with prospective hourly data collection through our electronic clinical information system, our study presents a

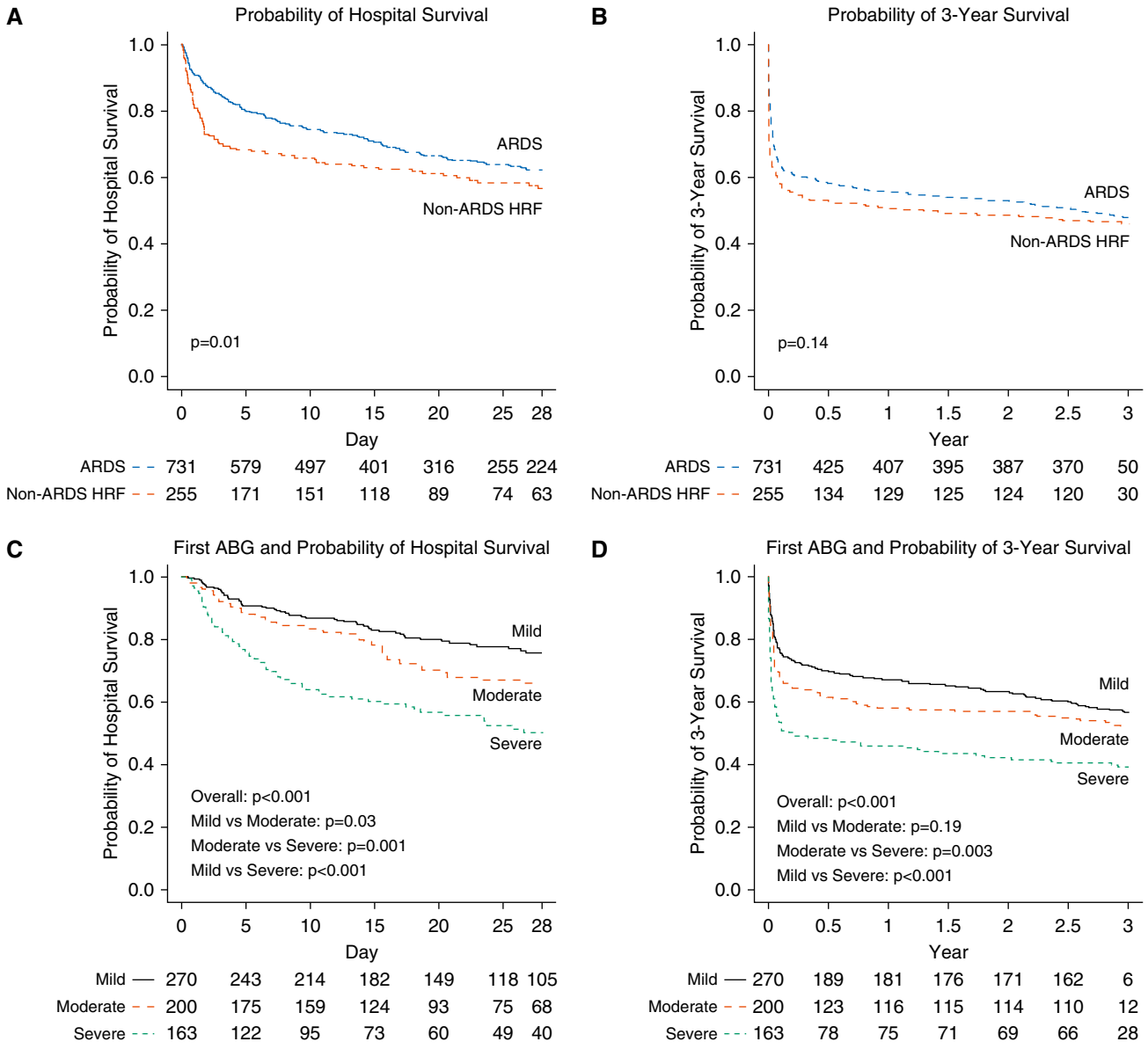

Figure 1. (*A–D*) Probability of survival in patients with hypoxemic respiratory failure and acute respiratory distress syndrome. ABG = arterial blood gas; ARDS = acute respiratory distress syndrome; HRF = hypoxemic respiratory failure.

detailed representation of mechanical ventilation practice in patients with hypoxemic respiratory failure and ARDS. Recent studies have suggested that mechanical power can be used to estimate the energy delivered to the patients by mechanical ventilation and in turn influence ventilator-induced lung injury (8, 29). A recent study demonstrated an association between mechanical power and outcome in critically ill patients (30). Our study provides an epidemiological description of mechanical power in ARDS and also suggests a mechanical power of >22 J/min is associated with lower 28-day hospital and 3-year mortality.

Key determinants of mechanical power are tidal volume and driving pressure. The median tidal volume (entire stay) in our patients was 8.0 ml/kg of PBW. Ventilating patients with median tidal volumes >8 ml/kg of PBW was not associated with increased mortality. This finding is supported by a recent systematic review that found no survival benefit with lower tidal volume strategy; however, it was noted that the larger the separation in tidal volume between the control and intervention groups, the higher the likelihood for benefit (31). Our observation may therefore be explained by a lack of spread between the highest and lowest tidal volume used, because 75% of patients with ARDS received 9.1 ml/kg of PBW or less. This is also supported by the recent LOTUS-FRUIT study, which modeled that lowering tidal volume to a lung-protective range in a group of patients with mixed acute respiratory failure (31% ARDS) was associated with a small to negligible effect on mortality (32).

Driving pressure is associated with mortality and is also one of the key

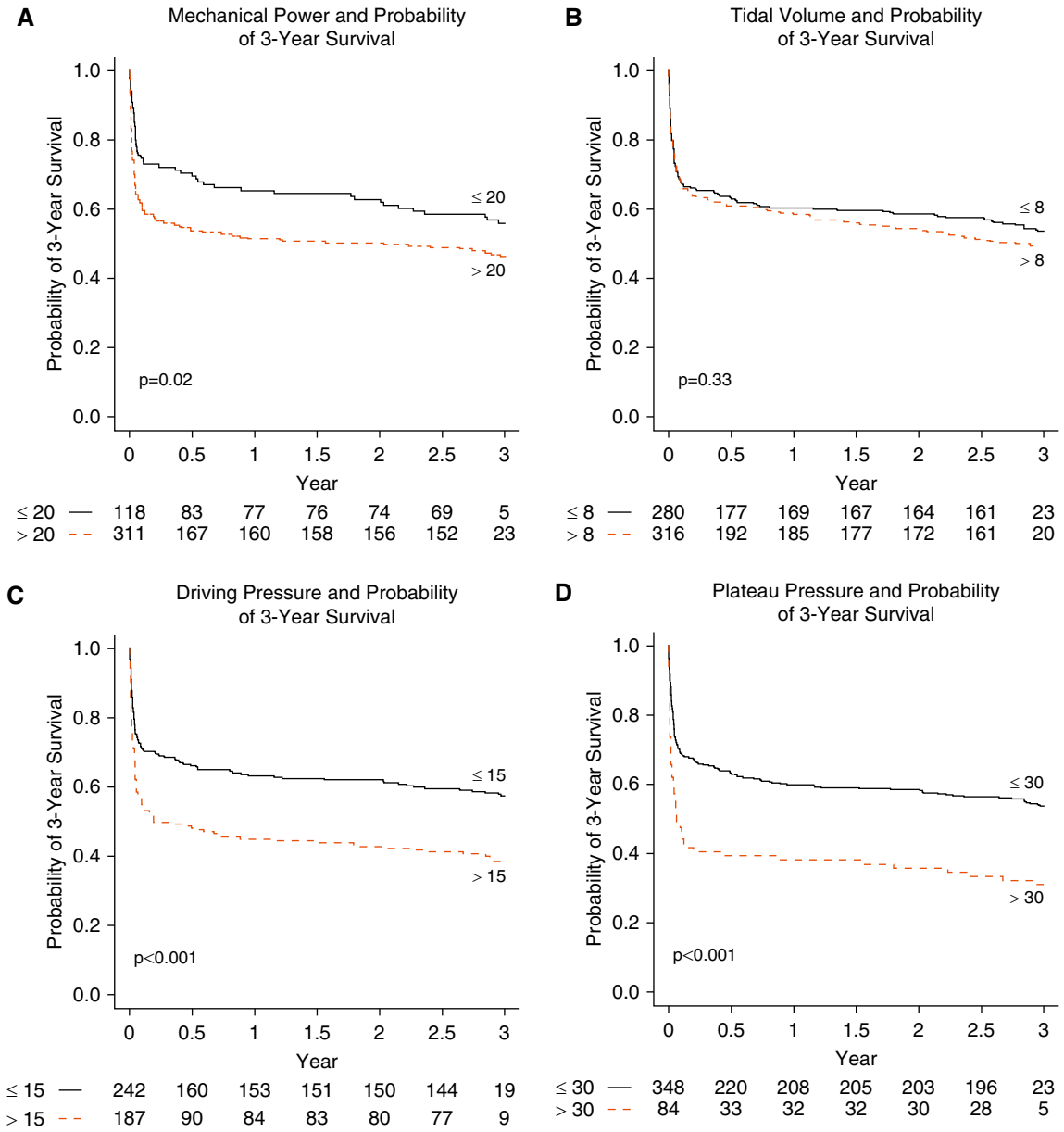

Figure 2. (*A–D*) Probability of 3-year survival in patients with acute respiratory distress syndrome by mechanical power and its determinants.

determinants of mechanical power (8, 9). In our study, higher driving pressure was associated with decreased 28-day hospital and 3-year survival. This is the first demonstration that driving pressure is associated with poor long-term outcomes. Given that driving pressure is a partially modifiable determinant of mechanical power (through manipulation of the tidal volume and PEEP) future studies may test if modulation of driving pressure can influence outcomes.

This is the first population-based estimate of the incidence and 3-year survival outcomes of Berlin definition ARDS using standardized screening. ARDS and non-ARDS hypoxemic respiratory failure survival rates are similar, despite patients with ARDS receiving more intense mechanical ventilation as demonstrated by a higher mechanical power. A previous study observed similar 60-day mortality between patients with ARDS and non-ARDS hypoxemic respiratory failure; however, it was limited by small patient numbers (ARDS), and no ventilator data (11). Previous studies examining 3-year outcomes in patients with ARDS are limited. A previous smaller single-center study looking only at patients with severe ARDS observed a survival rate of 55% at 3 years, which was much higher than our survival rate of 29.9% in severe ARDS (33). We observed that among those patients with ARDS who survived to hospital discharge, 77% survived to 3 years, which was lower when compared with the severe ARDS only cohort examined in the study by Khandelwal and coworkers (33).

Table 3. Ventilator-free days and length of stay outcomes by determinants of mechanical power in patients with ARDS

	Tidal Volume			Plateau Pressure			Driving Pressure			Mechanical Power		
	⩽8 ml/kg (*n* = 280)	>8 ml/kg (*n* = 316)	*P* Value	⩽30 cm H_2O (*n* = 348)	>30 cm H_2O (*n* = 84)	*P* Value	⩽15 (*n* = 242)	>15 (*n* = 187)	*P* Value	⩽22 J/min (*n* = 159)	>22 J/min (*n* = 270)	*P* Value
Ventilator-free days, median (IQR)	9 (0–20)	16 (0–22)	0.054	11 (0–20)	0 (0–14)	0.003	13 (0–20)	0 (0–17)	0.008	14 (0–21)	2 (0–17)	0.002
ICU-free days, median (IQR)	6 (0–16)	13 (0–18)	0.008	8 (0–16)	0 (0–12)	0.02	8 (0–17)	0 (0–14)	0.07	12 (0–19)	0 (0–14)	<0.001
ICU LOS, median (IQR)	13.0 (7.1–21.8)	10.6 (6.1–16.7)	0.054	13.0 (7.8–21.7)	12.5 (7.0–19.7)	>0.99	12.7 (7.7–20.6)	13.1 (7.9–22.2)	>0.99	12.4 (7.3–19.0)	13.8 (8.4–22.3)	>0.99
ICU mortality, *n* (%)	79 (28.2)	80 (25.3)	>0.99	94 (27.0)	41 (48.8)	0.002	60 (24.8)	75 (40.1)	0.01	31 (19.5)	104 (38.5)	0.001
Hospital LOS, median (IQR)	27.5 (16.0–50.5)	23.9 (14.6–42.0)	>0.99	25.1 (15.0–48.9)	23.9 (13.8–43.2)	>0.99	24.2 (13.9–46.7)	26.1 (15.3–46.4)	>0.99	25.8 (15.5–51.5)	24.6 (13.9–45.7)	>0.99

Definition of abbreviations: ARDS = acute respiratory distress syndrome; ICU = intensive care unit; IQR = interquartile range; LOS = length of stay.
All categorical data presented as number (percentage) and continuous data presented as median (interquartile range). *P* values are multiplied by 20 to account for *n* = 20 multiple comparisons (Bonferroni correction). Ventilator characteristics are median of the entire ICU stay.

ARDS incidence in our study was similar to that in other population-based studies that used the older AECC definition (12, 34, 35), including the KCLIP study from King County, Washington. Our study demonstrated an increase in the incidence of ARDS by age decile, similar to the KCLIP study. In addition, the most common ARDS etiologies within the KCLIP study and our study were similar (pulmonary sepsis, trauma, and aspiration). Admission Acute Physiology, Age, and Chronic Health Evaluation scores were higher in the KCLIP study than in our study. Our study also supports the findings in LUNG SAFE (Berlin definition) because the observed incidence per ICU bed per 4-week period in our study was similar (0.39 vs. 0.42) (2). This is an important validation because LUNG SAFE had only 14% (1,801 of 12,906) of its patients from Canada or the United States (36). LUNG SAFE was conducted over a 4-week period during winter months, thus potentially being influenced by seasonal variability (5, 20). We complement the LUNG SAFE results because we observed no seasonal variation in incidence between winter and nonwinter months over our 27-month study period. We hypothesize that seasonal increases in winter etiologies (e.g., viral pneumonia) may be offset by seasonal increases in nonwinter etiologies (trauma and pulmonary contusion during summer months). Data collected through this study were not able to distinguish viral pneumonia rates (from nonviral causes of pneumonia) and therefore this is a limitation of this study.

Strengths of our study include the prospective and standardized screening method, and rigorous data collection through the electronic clinical information system, allowing granular analysis of mechanical ventilation practice. Given that Calgary is a geographically distinct catchment area with all ICUs participating, this allowed us to define a population-based incidence. Limitations include the fact that it is an observational study using an unadjusted analysis, and thus associations with mortality do not prove causality. There is also a possibility that we underestimated the incidence if patients had incorrect or unknown postal codes or if they did not meet criteria

because of an ABG not being performed. Calgary is a populous urban city surrounded by a large rural catchment area. This may limit the generalizability to urban-only environments. Our *post hoc* application of the Berlin criteria (in lieu of the AECC criteria, which was initially used on some of the cohort) detracts from the prospective nature of the cohort. We also did not collect information from clinicians about their recognition of ARDS or their justification of the treatments that were instituted or withheld.

Conclusions

Using standardized screening, a large proportion of patients with hypoxemic respiratory failure met criteria for ARDS and subsequently sustained criteria for ARDS. Mechanical ventilation practice and mechanical power were associated with 28-day hospital and 3-year survival outcomes. Potentially modifiable determinants of mechanical power associated with outcome include P_{plat} and driving pressure. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Donna Kelly for her meticulous work during the chart review and data entry. The authors also thank Simon Guienguere for his help in data extraction from the clinical information system.

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