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Driving Pressure, Elastance, and Outcomes in a Real-World Setting: A Bi-Center Analysis of Electronic Health Record Data

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OBJECTIVES: Emerging evidence suggests the potential importance of inspiratory driving pressure (DP) and respiratory system elastance (E_{RS}) on outcomes among patients with the acute respiratory distress syndrome. Their association with outcomes among heterogeneous populations outside of a controlled clinical trial is underexplored. We used electronic health record (EHR) data to characterize the associations of DP and E_{RS} with clinical outcomes in a real-world heterogenous population.

DESIGN: Observational cohort study.

SETTING: Fourteen ICUs in two quaternary academic medical centers.

PATIENTS: Adult patients who received mechanical ventilation for more than 48 hours and less than 30 days.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: EHR data from 4,233 ventilated patients from 2016 to 2018 were extracted, harmonized, and merged. A minority of the analytic cohort (37%) experienced a Pao_2/Fio_2 of less than 300. A time-weighted mean exposure was calculated for ventilatory variables including tidal volume (V_T), plateau pressures (P_{PLAT}), DP, and E_{RS}. Lung-protective ventilation adherence was high (94% with $V_T < 8.5$ mL/kg, time-weighted mean $V_T = 6.8$ mL/kg, 88% with $P_{PLAT} \leq 30$ cm H_2O). Although time-weighted mean DP (12.2 cm H_2O) and E_{RS} (1.9 cm H_2O/[mL/kg]) were modest, 29% and 39% of the cohort experienced a DP greater than 15 cm H_2O or an E_{RS} greater than 2 cm H_2O/(mL/kg), respectively. Regression modeling with adjustment for relevant covariates determined that exposure to time-weighted mean DP (> 15 cm H_2O) was associated with increased adjusted risk of mortality and reduced adjusted ventilator-free days independent of adherence to lung-protective ventilation. Similarly, exposure to time-weighted mean E_{RS} greater than 2 cm H_2O/(mL/kg) was associated with increased adjusted risk of mortality.

CONCLUSIONS: Elevated DP and E_{RS} are associated with increased risk of mortality among ventilated patients independent of severity of illness or oxygenation impairment. EHR data can enable assessment of time-weighted ventilator variables and their association with clinical outcomes in a multicenter real-world setting.

Low tidal volume ventilation (LTVV) is the standard of care for patients with the acute respiratory distress syndrome (ARDS) and has been suggested as the appropriate management strategy for all ventilated patients (1–4). However, adherence to this strategy is low (5–7), limiting the ability to explore additive optimal ventilator management strategies outside of carefully controlled clinical trials. Recent secondary analyses of trial data have suggested that driving pressure (DP) and respiratory system elastance (E_{RS}) may be important parameters associated with outcomes among patients with ARDS receiving LTVV (8, 9) and raise the question of whether ventilation management

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KEY POINTS

Question: This cohort study was designed to use multicenter electronic health record (EHR) data to identify associations between driving pressure and elastance exposure and clinical outcomes in a heterogenous population not confined to acute respiratory distress syndrome (ARDS).

Findings: The analysis demonstrated that time-weighted exposure to an elevated driving pressure and elastance were associated with increased mortality. These associations persisted despite adjustment for demographics, severity of illness, and oxygenation impairment.

Meaning: This study's findings suggest the potential importance of driving pressure in outcomes for patients beyond just those with ARDS and demonstrated the utility of EHR data in multicenter investigations of ventilator care processes.

strategies should incorporate their consideration. Our understanding of these variables' distribution and their association with outcomes in an uncontrolled, heterogenous ventilated population is incomplete and limited in its generalizability (10, 11).

Electronic health records (EHRs) contain granular clinical data and are increasingly being used to study large populations of mechanically ventilated patients outside of clinical trials (12). EHR-derived datasets can contain all values of a given parameter such as DP or tidal volume (V_T); thus, they are often more comprehensive than clinical trial–derived datasets that may limit data capture to one or two values per study day. These comprehensive datasets enable more nuanced analyses of both adherence to guideline-based care and exposure to potentially harmful ventilator management strategies. Accordingly, EHR data can facilitate outcome associations between elastance and DP exposure in a real-world setting while avoiding practice misalignments observed in controlled clinical trials of titrated therapies (13).

Using a multicenter and multiyear EHR dataset, we examined the E_{RS} as well as the early exposure to LTVV and DP in a heterogenous ICU population who received mechanical ventilation, including subjects with and without ARDS. We sought to characterize ventilator management practices including DP utilization and adherence to LTVV outside of a controlled trial setting. Further, we leveraged the comprehensive nature of EHR data by determining the time-weighted exposure to ventilator settings early in the course of mechanical ventilation and these exposures' association with clinical outcomes independent of severity of illness or degree of hypoxemia.

STUDY DESIGN AND METHODS

This study was approved and granted a waiver of consent by the institutional review board (IRB) at the Medical University of South Carolina which also served as the IRB of record for Wake Forest University (IRB Pro00083096, approval date January 31, 2019). All procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975. We examined the EHR from hospitalizations of adults (age ≥ 18 yr old) who received invasive mechanical ventilation in any ICU for greater than or equal to 48 hours and less than or equal to 30 days in two large tertiary academic medical centers from 2016 to 2018. We excluded patients who received less than 48 hours or greater than 30 days of mechanical ventilation because these subjects were least likely to benefit or be harmed by mechanical ventilation practices. Further, we confined our analysis to patients who received full support modes (e.g., assist control modes, adaptive pressure control modes, synchronized intermittent mandatory ventilation, etc.) during the first 2 full days of mechanical ventilation because: 1) we wished to focus on the associations between ventilator settings and outcomes while minimizing the potential impact from spontaneous patient effort commonly seen in pressure support mode and 2) nonprotective V_Ts are infrequently changed after the first 2 days of mechanical ventilation (5, 12); thus, ventilator settings within this timeframe are representative of settings used throughout the duration of full support mode ventilation.

Data Collection and Harmonization Across Sites

EHR data including *International Classification of Diseases* (ICD) diagnosis and procedure codes, demographics, laboratory values, vital signs, height, weight,

medication usage, clinical outcomes, and length of stay were extracted from a pre-existing multicenter common data model (CDM) (14). Patients' records were extracted if they contained ICD, 10th Edition (ICD-10) codes for mechanical ventilation for at least 2 consecutive calendar days as well as a care location corresponding to an ICU on at least one calendar day. Additionally, serial ventilator setting data (e.g., mode, set V_T, set inspiratory pressure settings, FIO_2, set positive end-expiratory pressure [PEEP], and measured plateau pressures [P_{PLAT}]) and additional clinical variables (e.g., Glasgow Coma Scale [GCS] scores, daily urine output) were extracted for this cohort directly from the Epic Clarity databases of each institution and merged with CDM data. Data variables were reviewed for absence or greater than expected missingness, and, where appropriate, additional extractions were performed from Clarity. Site-specific datasets were then harmonized and merged. Time-stamped ventilator settings were reviewed and subjects who received mechanical ventilation for less than 48 continuous hours or greater than 30 calendar days were excluded from the analytic cohort.

Time-Weighted V_T, DP, and Elastance

All V_Ts were expressed as mL/kg of ideal body weight (IBW) using subject height and a standard equation (15). DP was calculated as the difference between P_{PLAT} and set PEEP ($DP = P_{PLAT} – PEEP$) measured at the same time point in volume control modes and as the inspiratory pressure for pressure control modes. Because the presence of spontaneous respiratory effort or auto-PEEP was not routinely discernible from EHR data, they were not included in the estimation of DP. Elastance was calculated as the quotient of DP and V_T ($E_{RS} = DP/V_T$) measured at the same time point. To quantify the exposure of each subject to V_T, DP, and E_{RS}, a time-weighted daily mean value was determined. Each instance of a variable was assigned a time value which corresponded to the interval between its measurement and the next time the variable was measured (e.g., a V_T of 7 mL/kg measured at 08:00 is assigned 4 hr if the next recorded V_T is at 12:00). Using these assigned time values, a time-weighted mean value was calculated for the first 2 fully ventilated calendar days (e.g., subject received 8 mL/kg of V_T for 18 hr and 6 mL/kg for 6 hr, the time-weighted mean exposure for that day = 7. 5 mL/kg). The time-weighted mean exposure on ventilator days 1 and 2 was then used for multivariable regression modeling as subsequently described.

Risk Adjustment and Missingness

To facilitate risk adjustment, demographics, ICD-10 codes, medication usage, and clinical variables were included in the extracted dataset. The ICD-10 codes were used to calculate a Charlson Comorbidity Index as previously described (16). Vital signs, laboratory values, vasopressor dosing, GCS, and urine output were analyzed from the first and second full calendar days of mechanical ventilation in order to calculate the six individual components of the Sequential Organ Failure Assessment (SOFA) score for these days. The missingness for each required variable was examined, determined to be acceptable, and addressed with multiple imputation by chained equations, using 25 multiply-imputed datasets—and imputing SOFA scores at the component level. Our prior research has shown imputation of SOFA component scores performed well under both missing at random and missing not at random missing data mechanisms, at missingness rates up to 40% (17). Ventilation variables were infrequently missing. V_T and PEEP were present in all subjects, whereas P_{PLAT}s were present in 90% of subjects on day 1. Missingness was addressed with multiple imputation as described above.

Statistical Analysis

Baseline characteristics of the population, including demographics, year of admission, and Charlson score, were summarized as means or medians, as appropriate. The time-weighted values of V_T, DP, E_{RS}, and PEEP were calculated for each subject and averaged by calendar day. The proportion of subjects who received guideline-recommended ventilation defined as a time-weighted V_T of less than or equal to 6. 5 mL/kg and less than or equal to 8. 5 mL/kg and P_{PLAT} less than or equal to 30 cm H_2O were determined. Similarly, the proportion of subjects who were exposed to a time-weighted DP greater than or equal to 15 cm H_2O or experienced a time-weighted E_{RS} greater than or equal to 2 cm H_2O/(mL/kg) were calculated.

Multivariable regression models were used to examine the associations between time-weighted DP and E_{RS} and in-hospital mortality. Adjusted relative risk estimates for mortality models were estimated using

Poisson regression with robust error variance. The primary exposures of time-weighted DP and time-weighted E_{RS} were modeled as dichotomous exposures of DP greater than or equal to 15 cm H_2O and E_{RS} greater than or equal to 2 cm H_2O/(ml/kg) on day 1 of mechanical ventilation. Multivariable models for mortality risk were adjusted for time-weighted V_T, time-weighted PEEP, subject demographics, comorbidity burden, site of care, SOFA score components, and type of ICU where care was provided (surgical vs medical). The day 1 values of V_T were used for adjustment except where not available in which day 2 values were substituted.

Time-weighted DP and E_{RS} were also examined for associations with ventilator-free days (within 28 d of onset of mechanical ventilation) and hospital length of stay using generalized linear regression models with negative binomial distribution and log link. Adjustment was again performed using the above demographic, clinical, location variables, and death.

All analyses were conducted with SAS Version 9.4 (SAS Institute, Cary, NC). All tests were two-sided with significance set a priori at α less than or equal to 0.05.

RESULTS

The EHR dataset consisted of 4,223 ventilator-dependent respiratory failure patients admitted across 14 ICUs predominantly comprised of older males of White and Black race (**Table 1**). Median Charlson and SOFA scores suggested a moderate comorbidity burden and a high level of acuity. Adherence to guideline-recommended lung-protective ventilation was high with 94% receiving V_T less than 8.5 mL/kg of IBW and 88.3% and 91.5% experiencing P_{PLAT} less than or equal to 30 cm H_2O on days one and two, respectively (**Fig. 1**).

Time-weighted mean V_T and the average daily maximum P_{PLAT} were consistent during the first 2 days of ventilation and were well within the boundaries of recommended settings (**Table 2**). Although the time-weighted mean DP (12.2 cm H_2O) and E_{RS} (1.9 cm H_2O/[mL/kg]) for the overall cohort were below the preselected inflection points, 29% of patients received a mean time-weighted DP greater than 15 cm H_2O, and 39% of patients experienced a mean time-weighted E_{RS} greater than 2 (cm H_2O/[mL/kg]) during the first day of mechanical ventilation. Consistent with its level of acuity and comorbidity, the cohort experienced prolonged need for mechanical ventilation and hospitalization and substantial mortality (28.8%).

TABLE 1.
Clinical Characteristics and Demographics of Ventilator-Dependent Respiratory Failure Patients

Clinical Characteristics	Value
Total cohort	4,223
Admission	
2016	1,774 (42.0)
2017	1,507 (35.7)
2018	942 (22.3)
Age, yr	60.0 (48.0–69.0)
Male	2,452 (58.1)
Race	
White	2,593 (61.4)
Black/African American	1,448 (34.3)
Asian	18 (0.4)
American Indian/Alaska Native	12 (0.3)
Hawaiian/Pacific Islander	5 (0.1)
Other	113 (2.7)
Unknown	34 (0.8)
Hispanic	84 (2.0)
Missing	19 (0.4)
Baseline Sequential Organ Failure Assessment score	11.0 (8.0–13.0)
Pao_2/Fio_2 ratio < 300 mm Hg	1,577 (37.3)
Charlson comorbidity index	3.0 (1.0–5.0)

All values listed as *n* (%) or median (interquartile range).

The associations between DP exposure and clinical outcomes are presented in **Table 3**. After multiple imputation and adjustment for relevant covariates, exposure to an elevated time-weighted mean DP (> 15 cm H_2O) was associated with a 19% increased risk of in-hospital mortality (adjusted relative risk [RR]: 1.19 [1.07–1.33]) and an average of 1.5 fewer ventilator-free days (12.4 [11.2–13.6] vs 13.9 d [13.1–14.6 d]). There was no difference in hospital length of stay (20.6 [19.5–21.7] vs 20.5 d [19.9–21.1 d]) when adjusting for death. To examine the potential impact of higher versus lower PEEP on the association between DP and mortality, we adjusted for an

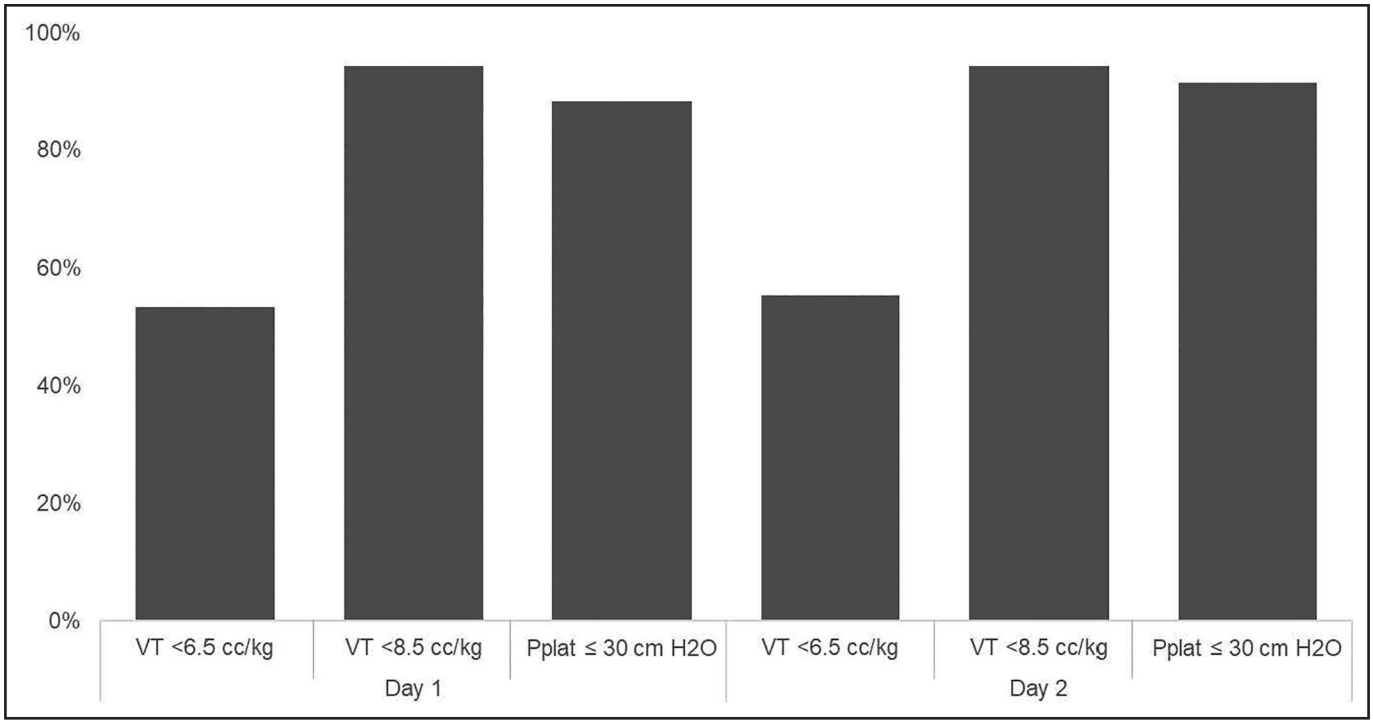

Figure 1. High adherence to lung-protective ventilation. The majority of subjects in the overall cohort received guideline-recommended lung-protective ventilation early in the course of mechanical ventilation. P_{PLAT} = plateau pressure, V_T = tidal volume.

interaction between PEEP greater than 12 cm H_2O and DP greater than 15 cm H_2O. Inclusion of this interaction had miminal impact on the association between the exposure to higher DP and mortality (RR 1.18 [1.05–1.34]). Outputs from multivariable models assessing the association between elastance and clinical outcomes are summarized in **Table 4**. Increased respiratory elastance (E_{RS} > 2 cm H_2O/mL/kg) was associated with a 13% increased risk of mortality (adjusted RR 1.13 [1.02–1.25]), whereas there was no difference in adjusted hospital length of stay or ventilator-free days ([20.4 (19.7–21.0) vs 20.8 d (20.0–21.8 d)] and [13.8 (13.0–14.6) vs 13.1 d (12.1–14.2 d)]), respectively.

DISCUSSION

Herein, we provide analysis that expands our understanding of the relationships between DP and E_{RS} and outcomes in patients with ventilator-dependent respiratory failure and highlights the potential of EHR data in critical care research. Using EHR records outside the context of a controlled trial, we confirmed that higher DP is independently associated with significantly higher risk of in-hospital mortality and fewer ventilator-free days, whereas higher E_{RS} is also associated with increased in-hospital mortality. These associations existed despite approximately 90% adherence to guideline-recommended (2) lung-protective ventilation practices and after adjustment for V_T and severity of illness. Further, they were identified in a heterogenous population, most of whom were unlikely to be receiving mechanical ventilation for ARDS based on observed Pao_2/Fio_2 ratios.

DP and elastance have recently been postulated to be important determinants of outcomes in patients receiving mechanical ventilation with ARDS (8, 9, 18–20). The two-part rationale for this hypothesis includes: 1) a recognition that E_{RS} can be used as a surrogate to adjust for the reduced functional lung size in ARDS (21) and 2) elevated DP may be a driver of ventilator-induced lung injury, independent of V_T, that quantifies the cyclical deformation imparted on the preserved, functional lung. This hypothesis has been supported by recent observational investigations of controlled clinical trial datasets. Amato et al (8) performed a secondary analysis of data from clinical trials examining ventilation practices in ARDS and determined that DP was more strongly associated with survival than traditional targets of lung-protective ventilation including V_T and P_{PLAT}. E_{RS} was later identified as a key mediator of the protective benefit of low V_T strategies observed

TABLE 2.
Early Respiratory Variables and Clinical Outcomes

Respiratory Variable or Outcome	Value
Time-weighted mean tidal volume (mL/kg ideal body weight)	
Day 1	6.8 ± 1.4 mL/kg
Day 2	6.7 ± 1.1 mL/kg
Maximum plateau pressure (cm H_2O)	
Day 1	20.0 ± 5.4
Day 2	19.7 ± 5.3
Time-weighted mean driving pressure (cm H_2O)	
Day 1	12.2 ± 4.7
Day 2	12.2 ± 4.7
Time-weighted mean driving pressure ≤ 15 cm H_2O	
Day 1[a]	3,015 (71.4)
Day 2[b]	3,073 (72.8)
Time-weighted mean elastance (cm H_2O/[mL/kg])	
Day 1	1.9 ± 1.6
Day 2	1.9 ± 1.8
Time-weighted mean elastance ≤ 2 cm H_2O/(mL/kg)	
Day 1[a]	2,521 (59.7)
Day 2[b]	2,579 (61.1)
Hospital length of stay (d)	15.0 (8.0–26.0)
Ventilator-free days	18 (0.0–23.0)
In-hospital mortality	1,218 (28.8)

All values listed as *n* (%), median (interquartile range), or mean ± SD.
[a]Missing data for *n* = 307 (7.3%).
[b]Missing data for *n* = 204 (4.8%).

TABLE 3.
Higher Driving Pressure Associated With Adjusted Risk of Mortality and Ventilator-Free Days

Outcome	DP ≤ 15 cm H_2O	DP > 15 cm H_2O	*p*
Relative risk of mortality[a] (95% CI)	Reference	1.19 (1.07–1.33)	0.001
Ventilator-free days at 28 d[a] (95% CI)	13.9 (13.1–14.6)	12.4 (11.2–13.6)	0.03
Hospital length of stay, d[b] (95% CI)	20.5 (19.9–21.1)	20.6 (19.5–21.7)	0.95

DP = driving pressure,
[a]Adjusted for age, minority status, site, surgical vs nonsurgical ICU, Charlson comorbidity index, time-weighted mean tidal volume, and Sequential Organ Failure Assessment (SOFA) score components.
[b]Adjusted for age, minority status, site, surgical vs nonsurgical ICU, Charlson comorbidity index, time-weighted mean tidal volume, SOFA score components, and death.

TABLE 4.
Higher Elastance Associated With Adjusted Risk of Mortality

Outcome	E_{RS} ≤ 2 cm H_2O/(mL/kg)	E_{RS} > 2 cm H_2O/(mL/kg)	*p*
Relative risk of mortality[a] (95% CI)	Reference	1.13 (1.02–1.25)	0.02
Ventilator-free days at 28 d[a] (95% CI), d	13.8 (13.0–14.6)	13.1 (12.1–14.2)	0.32
Hospital length of stay, d[b] (95% CI)	20.4 (19.7–21.0)	20.8 (20.0–21.8)	0.38

E_{RS} = respiratory system elastance.
[a]Adjusted for age, minority status, site, surgical vs nonsurgical ICU, Charlson comorbidity index, time-weighted mean tidal volume, and Sequential Organ Failure Assessment (SOFA) score components.
[b]Adjusted for age, minority status, site, surgical vs nonsurgical ICU, Charlson comorbidity index, time-weighted mean tidal volume, SOFA score components, and death.

in controlled clinical trials, further supporting the hypothesis that DP may be an important determinant of outcomes during ventilation of ARDS (9). Although unable to prove causality, these cumulative findings were thought-provoking and generated the unanswered questions of whether DP and E_{RS} are relevant in a non-ARDS population and whether these associations exist in a "real-world" setting outside of a clinical trial.

E_{RS} is frequently increased in ventilated patients without ARDS due to both chest wall (i.e., obesity, intra-abdominal hypertension) and lung (i.e., pneumonia, cardiogenic edema) pathologies with many of these conditions resulting in heterogenous distributions of cyclical strain (22–25). Thus, it stands to reason that DP may be relevant to outcomes in

ventilated patients without ARDS although existing data have been inconclusive perhaps related to differing approaches to ARDS surveillance and variable methodology to addressing missing data (10, 11, 26). To explore this hypothesis, we examined the associations between DP and E_{RS} and patient outcomes in a heterogenous population of critically ill patients including those cared for in medical, surgical, and other subspecialty ICUs. Although our data cannot readily identify which patients had ARDS, our broad inclusion criteria and epidemiologic estimates of ARDS prevalence (7) suggest that it was likely present in a minority of subjects. Furthermore, our associations between DP, E_{RS}, and outcomes support the hypothesis that DP is relevant to mechanical ventilation among patients with and without ARDS and may have practice implications for all mechanically ventilated patients. Thus, efforts to prospectively evaluate causality should include a broader cohort.

Clinical trial datasets are frequently constrained to one or two measures of a variable per study day in order to balance the need for relevant data with the time and labor required for high volume data capture. This can lead to incomplete characterization of clinical status and exposures, particularly in the ICU where physiology and treatments are dynamic. For example, a clinical trial dataset may contain one V_T or DP value per study day, often the maximum, minimum, or value closest to an arbitrary time point. By contrast, EHR-derived datasets can include every recorded value of these variables on a given study day allowing for a more robust and accurate estimation of ventilator setting exposure. In this work, we developed a time-weighted averaging methodology in order to estimate the cumulative exposure of individual subjects throughout a study day rather than assigning an exposure based on one recorded measurement. This approach helps to account for changes in ventilator settings and offers a surrogate adjustment for exposures to nonprotective settings. Future efforts to leverage EHR data and its analytic innovations in the execution of prospective ICU clinical trials are needed.

However, use of EHR-derived datasets can also result in challenges distinct from those encountered with datasets derived from clinical trials. The historical lack of widespread adoption of an EHR CDM across institutions has led to variability in how and where data are stored with resulting challenges in the extraction, harmonization, and merging of data from multiple sites. This is in contrast with clinical trial datasets which frequently use a standardized data capture template across sites allowing for easier harmonization and merging. Clinical trials also commonly protocolize the assessment of key variables and employ an iterative data review and query process to maximize data accuracy and minimize its missingness. Although EHR-derived datasets are less prone to the transcription errors encountered with manual data entry (27, 28), their reliance upon unprotocolized clinical data can lead to higher rates of missingness (29, 30). This study and others (31, 32) demonstrate that despite these challenges, EHR data can be effectively extracted from multiple sites and merged into an analytic dataset. Further, the rates of missingness were acceptable for addressing via multiple imputation.

This study has limitations that should be considered during interpretation. As noted, these results are observational and are potentially subject to bias; thus, they are unable to establish a causal relationship between DP or E_{RS} and outcomes. Additionally, as DP and E_{RS} are directly related, we are unable to state whether one variable is primarily responsible for the observed associations. Due to collinearity, we could not adjust for one to assess for a residual, independent association with the other. Our use of a time-weighted average will partially account for periods of time that a subject may have received nonprotective ventilation but does not allow for granular quantification of how much time they received it. This exposure time may be an important contributor to negative outcomes (12). It is possible that the missing data inherent with EHR-derived datasets could introduce bias into the analysis. To mitigate this, we used validated imputation methodology and confirmed that the degree of missingness was within the acceptable boundaries of this approach. Finally, cyclical lung strain may be related to mechanical power and may be exacerbated during active or discordant respiration (33, 34). As flow rates and ventilator dyssyncrony are seldom, if ever, recorded in structured EHR data, we were unable to adjust for these potential confounders. Future investigation into the use of natural language processing or ventilator waveform analysis to identify these potentially relevant contributors could augment the utility of mechanical ventilation-focused EHR-derived datasets. Similarly, these datasets' value will also be enhanced

through the application of deep learning methodology to identify ARDS (35).

INTERPRETATION

Exposures to higher DP and E_{RS} are associated with worse patient outcomes among heterogenous populations of mechanically ventilated patients. These findings suggest that future efforts to prospectively validate a causal impact of driving pressure should focus on diverse cohorts rather than a narrowly defined population of patients with ARDS. EHR data offer the ability to accurately estimate longitudinal exposures in the ICU and can facilitate observational investigation of mechanical ventilation-related care processes.

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