OBSERVATIONAL STUDY

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Elevated Driving Pressure and Elastance Does Not Increase In-Hospital Mortality Among Obese and Severely Obese Patients With Ventilator Dependent Respiratory Failure

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IMPORTANCE: Existing recommendations for mechanical ventilation are based on studies that under-sampled or excluded obese and severely obese individuals.

OBJECTIVE: To determine if driving pressure (DP) and total respiratory system elastance (E_{rs}) differ among normal/overweight (body mass index [BMI] < 30 kg/m^2), obese, and severely obese ventilator-dependent respiratory failure (VDRF) patients and if there any associations with clinical outcomes.

DESIGN, SETTING, AND PARTICIPANTS: Retrospective observational cohort study during 2016–2018 at two tertiary care academic medical centers using electronic health record data from the first 2 full days of mechanical ventilation. The cohort was stratified by BMI classes to measure median DP, time-weighted mean tidal volume, plateau pressure, and E_{rs} for each BMI class.

SETTING AND PARTICIPANTS: Mechanically ventilated patients in medical and surgical ICUs.

MAIN OUTCOMES AND MEASURES: Primary outcome and effect measures included relative risk of in-hospital mortality, ventilator-free days, ICU length of stay, and hospital length of stay with multivariable adjustment.

RESULTS: The cohort included 3,204 patients with 976 (30.4%) and 382 (11.9%) obese and severely obese patients, respectively. Severe obesity was associated with a DP greater than or equal to 15 cm H_2O (relative risk [RR], 1.51 [95% CI, 1.26–1.82]) and E_{rs} greater than or equal to 2 cm H_2O/(mL/kg) (RR, 1.31 [95% CI, 1.14–1.49]). Despite elevated DP and E_{rs}, there were no differences in in-hospital mortality, ventilator-free days, or ICU length of stay among all three groups.

CONCLUSIONS AND RELEVANCE: Despite higher DP and E_{RS} among obese and severely obese VDRF patients, there were no differences in in-hospital mortality or duration of mechanical ventilation, suggesting that DP has less prognostic value in obese and severely obese VDRF patients.

KEY WORDS: artificial respiration; critical care; morbid obesity; obesity; respiratory insufficiency

As of 2018, the age-adjusted prevalence of obesity in the United States had increased to 42.4% of the population with 9.2% considered severely obese (1). While obesity remains a public health crisis, various studies in medical and surgical critically illness have found a survival advantage among obese patients, coined "the obesity paradox" (2–4). Existing meta-analyses and observational cohort studies have found a higher risk of ventilator-dependent respiratory failure (VDRF) and acute respiratory distress syndrome (ARDS) among obese and severely obese, despite no difference in mortality

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KEY POINTS

Question: Does driving pressure (DP) differ in obese and severely obese patients requiring mechanical ventilation from normal and overweight patients and is an elevated DP (≥ 15 cm of H_2O) associated with worse clinical outcomes in this population?

Findings: In this large, bicenter retrospective cohort study, DP was significantly higher among obese and severely obese patients requiring mechanical ventilation for any reason. There were no differences in mortality among all body mass index classes.

Meaning: Although elevated DP is common among obese and severely obese patients requiring mechanical ventilation, it is less prognostic of poor outcomes than previously seen among normal weight and overweight individuals and likely is influenced by under-recruitment with existing lung protective ventilation practices.

(5–9). While the obesity paradox remains unsettled, as contradictory data exist in severely obese individuals with COVID-19 pneumonia, how obesity influences clinical outcomes in VDRF remains uncertain (10, 11).

Present guidelines for mechanical ventilation of ARDS recommend using lung protective ventilation (LPV) consisting of low tidal volume (Vt) ventilation (between 4 and 8 cc/kg of ideal body weight) with plateau pressure (P_{plat}) less than 30 cm H_2O regardless of body mass index (BMI) (12). Studies of LPV in VDRF without ARDS have found similar benefits as well, suggesting that LPV should be the standard ventilation strategy for all mechanically ventilated patients (13, 14). Efforts to better understand why LPV improves mortality in VDRF have identified a linear correlation between driving pressure (DP) and mortality in the setting of ARDS, suggesting that lung compliance may mediate the benefit of LPV in ARDS. However, observational studies in obese patients have presented mixed results finding no clear association between DP and mortality in ARDS but supporting the hypothesis that the respiratory mechanics of obese and severely obese patients differ from normal weight patients (15, 16). Furthermore, severely obese subjects were either under-sampled or explicitly excluded from existing studies of LPV in ARDS and non-ARDS (13, 14, 17–19). Thus, current mechanical ventilation strategies in obese populations are extrapolated from data in mostly normal weight and overweight individuals despite evidence suggesting that pulmonary mechanics in severely obese individuals differ from normal and overweight individuals (15). An optimal DP for obese and severely obese VDRF patients remains uncertain.

Few studies have examined how differences in ventilator mechanics among obese and normal weight individuals affect clinical outcomes, particularly in the setting of the heterogenous pathophysiology seen in clinical practice. In this study, we used a bicenter, retrospective cohort of patients with VDRF to measure differences in DP and total respiratory system elastance (E_{rs}) among normal/overweight, obese, and severely obese patients. Second, we sought to determine whether clinical outcomes would differ across each BMI group.

METHODS

This study was approved by the Medical University of South Carolina (MUSC) institutional review board (IRB) and served as the IRB of record for Wake Forest (WF) 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.

Data Collection and Harmonization Across Sites

Electronic health record (EHR) hospitalization data from MUSC hospital and WF Baptist Medical Center were extracted using a preexisting federated common data model (CDM) (20). Data for our cohort were assembled by linking data from the Carolinas Collaborative CDM to additional clinical data from Epic Clarity databases (Verona, WI) from MUSC and WF Baptist Health. EHR data was queried for diagnostic and procedure codes for mechanical ventilation for at least 2 consecutive calendar days and a care location corresponding to an ICU for at least 1 calendar day. All patients requiring mechanical ventilation were included, irrespective of their reason for requiring mechanical ventilation. *International Classification of*

Diseases, 9th Revision and 10th Revision diagnosis and procedure codes, demographics, laboratory values, vital signs, height, weight, medication usage, and clinical outcomes were extracted from the Carolinas Collaborative CDM. Time-stamped ventilator settings and additional nursing observations were extracted from MUSC and WF Epic Clarity databases, respectively. CDM datasets were enriched with additional data from institutional Epic Clarity databases to limit data missingness as applicable by each individual site. Adults greater than or equal to 18 years old who received invasive mechanical ventilation in an ICU for greater than or equal to 48 hours and less than or equal to 30 days between 2016 and 2018 at both academic medical centers were included. Additionally, we confined our analysis to patients receiving full ventilatory support (i.e., not a weaning mode) during the first 2 full days to minimize confounding from patient-ventilator interactions and assuming early ventilator settings would approximate settings used throughout the duration of mechanical ventilation (21, 22).

Ventilator Parameters

Vts were normalized to ideal body weight according to standard equations from the ARDS Network trial (23). DP was calculated as the difference between P_{plat} and positive end-expiratory pressure (PEEP) ($DP = P_{plat}–PEEP$). E_{rs} was calculated by dividing DP by Vt ($E_{rs} = DP/Vt$) adjusted for ideal body weight. Both DP and E_{rs} were calculated using data from synchronous time points. Due to limitations in the available data, we could not account for spontaneous breathing efforts, airway closure phenomena, or auto-PEEP and their potential contributions to DP and E_{rs}. Time-weighted daily mean values were derived by calculating a mean daily value for each ventilator parameter weighted for the duration of time spent at a given setting as recorded in the EHR. Values for the first and second full days of mechanical ventilation were used in the analyses.

Risk Adjustment and Data Missingness

Outcome measures were adjusted for comorbid conditions using the Charlson Comorbidity Index (CCI) and for acuity of illness using the Sequential Organ Failure Assessment (SOFA) score (24, 25). Data missingness was addressed using multiple imputation by chained equations in all multivariable models using previously developed methods (26). SOFA score components were imputed using 25 multiply imputed datasets. The fraction of missing SOFA score components are presented in **Table S5** (http://links.lww.com/CCX/B107).

Statistical Analysis

The primary exposure variable was a stratified BMI class. Cohort members with a BMI between 18.5 kg/m^2 and less than 30 kg/m^2, 30.0 kg/m^2 and less than 40 kg/m^2, and 40.0 kg/m^2 or greater were classified as "Normal or Overweight," "Obese," and "Severely Obese," respectively. Participants with BMI less than 18.5 kg/m^2 were excluded from the analysis. The primary outcome variable was in-hospital mortality. Secondary outcomes include ICU length of stay (LOS), hospital LOS, and ventilator-free days at 28 days. Primary and secondary outcomes were determined a priori.

Baseline characteristics of the population, including demographics, year of admission, BMI, CCI, SOFA scores, Pao_2/Fio_2 ratios, and time-weighted mean ventilator parameters, were summarized using descriptive statistics. Mean and median values with corresponding sd and interquartile range were reported for normal and non-normal data, respectively. Normality was assessed using the Kolmogorov-Smirnov test. Between-group comparisons were performed using chi-square or Kruskal-Wallis tests, as appropriate.

Multivariable Modeling

Multivariable models measuring associations between BMI classes and in-hospital mortality were created using Poisson regression with robust error variance. The relative risk (RR) of mortality for obese and severely obese BMI classes were adjusted with the following covariables: age, time-weighted mean DP greater than or equal to 15 cm H_2O or E_{rs} greater than or equal to 2 cm H_2O/(mL/kg), sex, minority status, surgical ICU location, CCI, time-weighted mean Vt, and SOFA score components following multiple imputation. The RR of each BMI class to experience a median time-weighted mean DP greater than or equal to 15 cm H_2O or E_{rs} greater than or equal to 2 cm H_2O/(mL/kg) was estimated using Poisson regression with robust error variance and adjusted for sex, minority status, surgical ICU location, and SOFA score components following multiple imputation. When calendar day 1, Vt was not available, calendar day 2, Vt was used instead. DP

and E_{rs} were modeled as dichotomous variables due to existing literature supporting a low likelihood of mortality benefit when DP less than 15 cm H_2O (27).

Associations between BMI classes and ventilator days, ventilator-free days within 28 days of onset of mechanical ventilation, ICU LOS, and hospital LOS were estimated using generalized linear regression models with negative binomial distribution and log link. Models estimating ventilator-free days were adjusted for age, sex, minority status, surgical ICU location, CCI, multiply imputed SOFA score components, time-weighted mean DP greater than or equal to 15 cm H_2O, and time-weighted mean Vt. All other models were adjusted for age, sex, minority status, site, surgical ICU location, CCI, SOFA score components, time-weighted mean DP greater than or equal to 15 cm H_2O, time-weighted mean Vt, and in-hospital mortality.

Covariables included for adjustment were selected a priori based on clinical significance and hypothesized causal relationships. Given the missingness present in our dataset, we completed a sensitivity analysis using complete case analysis (CCA) for multivariable RR models for in-hospital mortality, DP greater than or equal to 15 cm H_2O, and E_{rs} greater than or equal to 2 cm H_2O/(mL/kg). All analyses and modeling were performed using SAS 9.4 (Cary, NC). All tests were two-sided with significance set a priori at α less than 0.05.

RESULTS

The cohort consisted of 3,204 patients with VDRF with a median BMI of 28.5 kg/m^2. There was a predominance of White patients (63.3%) with a significant minority of African American (32.1%) (**Table 1**). The median baseline SOFA scores and CCI suggest a high level of acuity and moderate burden of comorbid conditions (Table 1).

Adherence to LPV was high in all BMI categories with median time-weighted mean Vt of 6.5 mL/kg (6.1–7.2 mL/kg) and 6.4 mL/kg (6.0–7.1 mL/kg) and median maximum P_{plat} of 22.0 cm H_2O (18.0–27.0 cm H_2O) and 21.0 cm H_2O (18.0–26.0 cm H_2O) for the entire cohort on day 1 and day 2 of mechanical ventilation, respectively (**Table 2**). Sixty percent, 64.7%, and 65.4% of patients in the normal/overweight (BMI < 30 kg/m^2), obese (BMI 30–39.9 kg/m^2), and severely

TABLE 1.
Patient Characteristics

Clinical Characteristics	Total Cohort (*n* = 3,204)	< 30 kg/m^2 (*n* = 1,846)	30–39.9 kg/m^2 (*n* = 976)	≥ 40 kg/m^2 (*n* = 382)	*p*
Admission year					0.2357
2016	1,198 (37.4)	676 (36.6)	369 (37.8)	153 (40.1)	
2017	1,257 (39.2)	714 (38.7)	389 (39.9)	154 (40.3)	
2018	749 (23.4)	456 (24.7)	218 (22.3)	75 (19.6)	
Age, yr	59.0 (47.0–69.0)	60.0 (46.0–70.0)	61.0 (50.0–70.0)	56.0 (45.0–64.0)	0.0002
Male	1,883 (58.8)	1,145 (62.0)	567 (58.1)	171 (44.8)	< 0.0001
Race					0.0011
African American	1,027 (32.1)	596 (32.3)	277 (28.4)	154 (40.3)	
Unknown/Other	149 (4.7)	88 (4.8)	45 (4.6)	16 (4.2)	
White	2,028 (63.3)	1,162 (62.9)	654 (67.0)	212 (55.5)	
Hispanic	71 (2.2)	40 (2.2)	24 (2.5)	7 (1.8)	0.7603
Body mass index (kg/m^2)	28.5 (23.9–34.2)	24.7 (21.8–27.2)	33.5 (31.7–36.0)	46.0 (42.4–51.2)	< 0.0001
Baseline Sequential Organ Failure Assessment score	10.0 (8.0–13.0)	10.0 (8.0–13.0)	10.0 (8.0–13.0)	10.0 (8.0–13.0)	0.7972
Charlson Comorbidity Index	3.0 (1.0–5.0)	3.0 (1.0–5.0)	3.0 (1.0–6.0)	4.0 (2.0–6.0)	0.0002

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

TABLE 2.
Respiratory and Ventilator Parameters Stratified by Body Mass Index

Ventilator Parameters	Total ($n = 3,204$)	BMI < 30 kg/m² ($n = 1,847$)	BMI 30–39.9 kg/m² ($n = 975$)	BMI ≥ 40 kg/m² ($n = 382$)	p
Pao_2/Fio_2 ratio < 300 mm Hg, n (%)[a]	1,989 (62.1)	1,108 (60.0)	631 (64.7)	250 (65.4)	< 0.0001
Time-weighted mean tidal volume (mL/kg)					
Day 1	6.5 (6.1–7.2)	6.4 (6.0–7.1)	6.5 (6.1–7.4)	6.6 (6.1–7.6)	< 0.0001
Day 2	6.4 (6.0–7.1)	6.3 (6.0–7.0)	6.4 (6.1–7.2)	6.4 (6.1–7.4)	< 0.0001
Time-weighted mean positive end-expiratory pressure (cm H_2O)					
Day 1	8.0 (5.0–8.8)	8.0 (5.0–8.0)	8.0 (5.3–9.4)	8.0 (5.9–10.0)	< 0.0001
Day 2	8.0 (5.0–8.5)	8.0 (5.0–8.0)	8.0 (5.0–8.9)	8.0 (5.2–10.0)	< 0.0001
Maximum plateau pressure (cm H_2O)					
Day 1	22.0 (18.0–27.0)	21.0 (18.0–25.0)	22.0 (19.0–27.0)	25.0 (21.0–29.0)	< 0.0001
Day 2	21.0 (18.0–26.0)	20.0 (17.0–25.0)	22.0 (19.0–26.0)	26.0 (21.0–29.0)	< 0.0001
Time-weighted mean driving pressure (cm H_2O)					
Day 1	11.8 (9.0–15.0)	11.1 (8.8–14.5)	12.0 (9.6–15.0)	13.9 (10.7–17.7)	< 0.0001
Day 2	11.4 (9.0–14.5)	10.9 (8.6–13.9)	11.8 (9.3–14.7)	13.4 (10.7–16.8)	< 0.0001
Driving pressure ≥ 15 cm H_2O, n (%)					
Day 1[b]	673 (21.0)	343 (18.6)	208 (21.3)	122 (31.9)	< 0.0001
Day 2[c]	658 (20.5)	321 (17.4)	218 (22.3)	119 (31.2)	< 0.0001
Time-weighted mean elastance (cm H_2O/[mL/kg])					
Day 1	1.7 (1.3–2.3)	1.7 (1.3–2.2)	1.8 (1.4–2.3)	2.0 (1.6–2.6)	< 0.0001
Day 2	1.7 (1.3–2.2)	1.7 (1.3–2.2)	1.8 (1.4–2.2)	2.0 (1.5–2.5)	< 0.0001
Elastance ≥ 2 cm H_2O/(mL/kg), n (%)					
Day 1[d]	935 (29.2)	498 (27.0)	290 (29.7)	147 (38.5)	< 0.0001
Day 2[e]	1,041 (32.5)	537 (29.1)	339 (34.7)	165 (43.2)	< 0.0001

BMI = body mass index.
[a]Missing data $n = 733$ (22.9%).
[b]Missing data $n = 660$ (20.6%).
[c]Missing data $n = 257$ (8.0%).
[d]Missing data $n = 660$ (20.6%).
[e]Missing data $n = 257$ (8.0%).
All values are listed as n (%) or median (interquartile range).

obese (BMI > 40 kg/m²) strata had Pao_2/Fio_2 less than 300 mm Hg, respectively (Table 2). The median time-weighted mean PEEP was 8 cm H_2O for all three BMI classes with a significantly higher range among subjects in higher BMI classes (Table 2). While the median PEEP was consistent across all three subgroups, the median maximum P_{plat} increased incrementally across BMI strata for both day 1 and day 2 of mechanical ventilation (Table 2).

DP increased incrementally across each BMI class. Median day 1 time-weighted mean DP was 11.1 cm H_2O (8.8–14.5 cm H_2O), 12.0 cm H_2O (9.6–15.0 cm H_2O), and 13.9 cm H_2O (10.7–17.7 cm H_2O) for the normal/overweight (BMI < 30 kg/m²), obese (BMI 30–39.9 kg/m²), and severely obese (BMI > 40 kg/m²) groups, respectively ($p < 0.0001$) (Table 2). Similarly, median day 2 time-weighted mean DP was 10.9 cm H_2O (8.6–13.9 cm H_2O), 11.8 cm H_2O (9.3–14.7 cm H_2O), and 13.4 cm H_2O (10.7–16.8 cm H_2O) for the normal/overweight, obese, and severely obese groups, respectively ($p < 0.0001$) (Table 2). Proportionally, 18.6%, 21.3%, and 31.9% of patients in the normal/

TABLE 3.
Adjusted Clinical Outcomes Stratified by Body Mass Index

Clinical Outcomes	BMI < 30 kg/m²	BMI 30–39.9 kg/m²	BMI ≥ 40 kg/m²
High driving pressure[a] (RR)[b]	Reference	1.20 (1.03–1.40)[c]	1.51 (1.26–1.82)[d]
High respiratory system elastance[e] (RR)[b]	Reference	1.12 (1.01–1.25)[c]	1.31 (1.14–1.49)[d]
In-hospital mortality (RR)[f]	Reference	0.93 (0.81–1.05)	0.99 (0.82–1.19)
Ventilator days[g]	8.1 (7.8–8.5)	8.1 (7.7–8.5)	7.8 (7.3–8.4)
28-d ventilator-free days[h,f]	19.1 (18.7–19.5)	19.3 (18.7–19.9)	19.5 (18.7–20.4)
ICU LOS (d)[g]	11.2 (10.8–11.6)	11.1 (10.6–11.7)	10.8 (10.1–11.6)
Hospital LOS (d)[g]	19.4 (18.5–20.3)	18.1 (17.2–19.1)[c]	17.0 (15.7–18.4)[c]

BMI = body mass index, LOS = length of stay, RR = relative risk.

[a]High driving pressure (DP) ≥ 15 cm H_2O.

[b]Model adjusted for age, sex, minority status, site, surgical vs nonsurgical ICU, Charlson Comorbidity Index, Sequential Organ Failure Assessment (SOFA) score components, and in-hospital mortality.

[c]$p < 0.05$.

[d]$p < 0.0001$.

[e]High respiratory system elastance: ≥ 2 cm H_2O/(mL/kg).

[f]Model adjusted for age, sex, minority status, surgical vs nonsurgical ICU, Charlson Comorbidity Index, SOFA score components, DP ≥ 15 cm H_2O, and time-weighted mean tidal volume.

[g]Model adjusted for age, sex, minority status, site, surgical vs nonsurgical ICU, Charlson Comorbidity Index, SOFA score components, high DP, mean tidal volume, and in-hospital mortality.

[h]Among those who survived their index admission ($n = 2{,}384$).

All models were reported as a point estimate (95% CI). BMI < 30 kg/m² category was used as a referent for all pairwise comparisons.

overweight, obese, and severely obese categories had a time-weighted mean DP greater than or equal to 15 cm H_2O on day 1 (Table 2). Patients with severe obesity had a 51% higher (RR, 1.51; 95% CI, 1.26–1.82) RR of having a time-weighted mean DP greater than or equal to 15 cm H_2O after adjustment for sex, minority status, SOFA score components, and surgical ICU location (**Table 3**; unadjusted values listed in **Table S1**, http://links.lww.com/CCX/B107).

Similarly, unadjusted E_{rs} increased with each BMI class. The day 1 median time-weighted mean E_{rs} was 1.7 cm H_2O/(mL/kg) (1.3–2.3 cm H_2O/[mL/kg]), 1.8 cm H_2O/(mL/kg) (1.4–2.3 cm H_2O/[mL/kg]), and 2.0 cm H_2O/(mL/kg) (1.6–2.6 cm H_2O/[mL/kg]) for the normal/overweight, obese, and severely obese groups, respectively ($p < 0.0001$) (Table 2). Day 2 median time-weighted variables were similar to day 1 and listed in Table 2. The proportions of each BMI class with a time-weighted mean E_{rs} greater than or equal to 2 cm H_2O/(mL/kg) were 27.0%, 29.7%, and 38.5% for normal/overweight, obese, and severely obese groups, respectively ($p < 0.0001$) (Table 2). In each group, this proportion increased to 29.1%, 34.7%, and 43.2%, respectively, on day 2 of mechanical ventilation ($p < 0.0001$) (Table 2). Patients with severe obesity had a 31% higher (RR, 1.31; 95% CI, 1.14–1.49) RR of having an E_{rs} greater than or equal to 2 cm H_2O/(mL/kg) after adjustment for sex, minority status, SOFA score components, and surgical ICU location (Table 3; unadjusted values listed in Table S1, http://links.lww.com/CCX/B107).

Despite exposure to higher DP among the obese and severely obese groups, in-hospital mortality was similar among all three BMI classes (**Fig. 1**). Unadjusted and adjusted ventilator days, 28-day ventilator-free days, and ICU LOS were similar among all three BMI classes (Table 3; unadjusted values listed in Table S1, http://links.lww.com/CCX/B107). Despite similar ICU LOS, median hospital LOS was shorter for severely obese and obese patients compared with normal/overweight patients (Table 3; unadjusted values listed in Table S1, http://links.lww.com/CCX/B107). Neither obesity nor severe obesity was associated with increased in-hospital mortality after adjustment for age, sex, minority status, SOFA score components, CCI, time-weighted mean V_T, and DP greater than or equal to 15 cm H_2O or E_{rs} greater than or equal to 2 cm H_2O/(mL/kg) (**Fig. 2**; Numeric RR estimates listed in **Table S3** and **Table S4** http://links.lww.com/CCX/B107). Sensitivity analysis using CCA was notable for no statistically significant differences between point estimates from

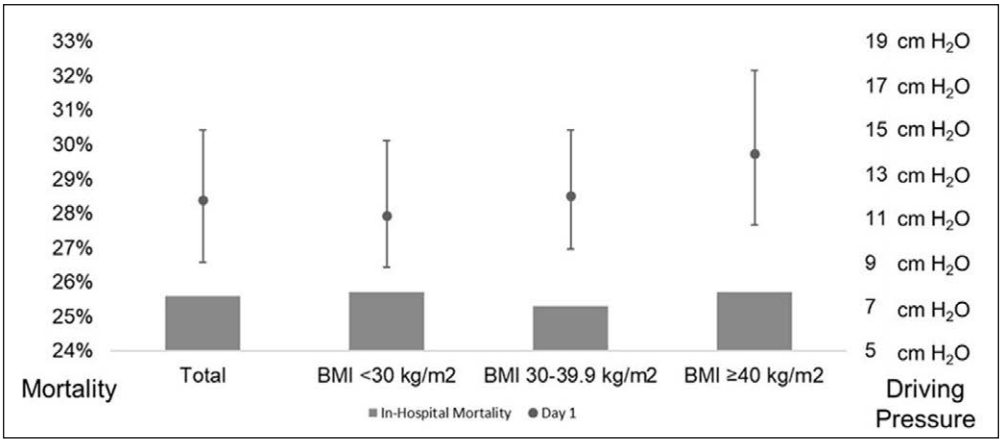

Figure 1. Median driving pressure (DP) increases with obesity without increasing mortality. The median time-weighted mean DP for the entire cohort was 11.8 cm H_2O (9–15 cm H_2O). Median time-weighted mean DP progressively increased with higher body mass index (BMI) classes (11.1 cm H_2O [8.8–14.5 cm H_2O], 12.0 cm H_2O [9.6–15.0 cm H_2O], and 13.9 cm H_2O [10.7–16.8 cm H_2O] for BMI < 30 kg/m^2, BMI 30–39.9 kg/m^2, and BMI > 40 kg/m^2 groups, respectively). Despite increasing DP, there was no difference in in-hospital mortality among all three groups. Overall in-hospital mortality was 25.6% with 25.7%, 25.3%, and 25.7% for BMI less than 30 kg/m^2, BMI 30–39.9 kg/m^2, and BMI greater than 40 kg/m^2 groups, respectively.

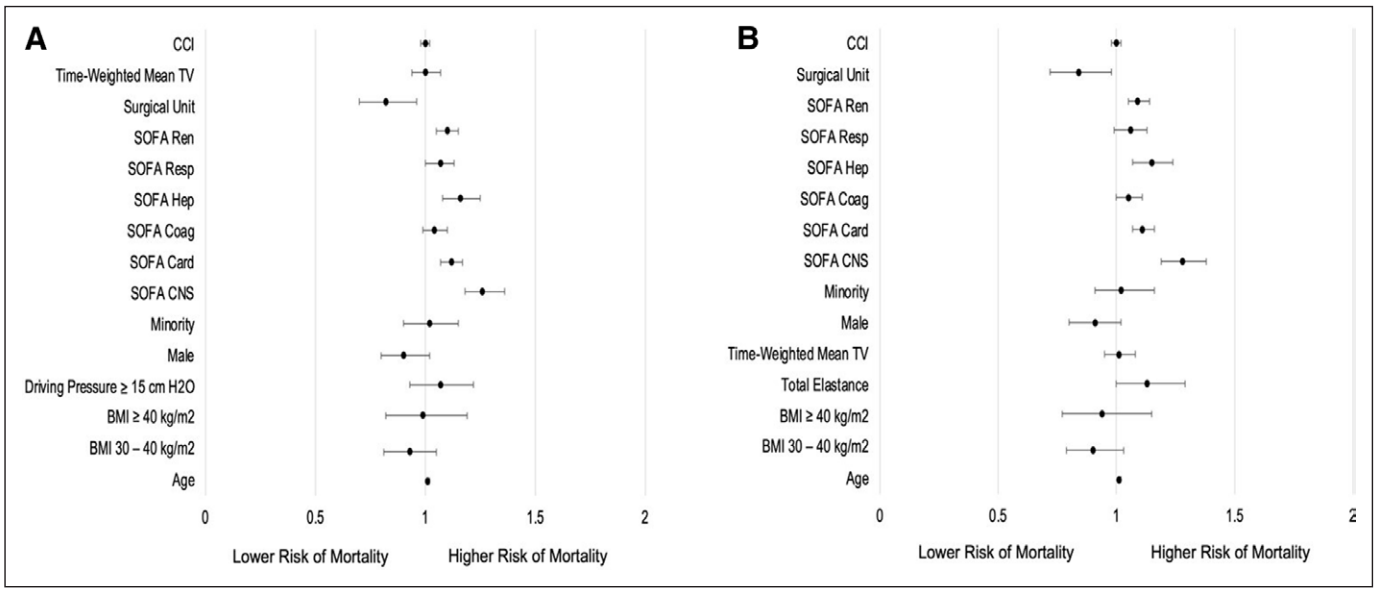

Figure 2. Worsening obesity was not associated with increased relative risk of mortality after adjusting for elevated driving pressure or total elastance. After adjusting for Sequential Organ Failure Assessment (SOFA) score components, Charlson Comorbidity Index (CCI), time-weighted mean tidal volume (TV), sex, minority status, age, and driving pressure greater than or equal to 15 cm H_2O (**A**) or total elastance greater than or equal to 2 cm H_2O/(mL/kg) (**B**) obesity was not associated with worsening mortality. BMI = body mass index, Card = cardiology, Coag = coagulation, Hep = hepatology, Ren = renal, Resp = respiratory.

models using imputed data versus CCA, although CCA models had wider CIs as expected (**Table S2**, http://links.lww.com/CCX/B107).

DISCUSSION

In a large bicenter retrospective study using EHR-derived clinical data, we found that obesity and severe obesity were associated with higher DP and E_{rs} but were not associated with differences in in-hospital mortality, 28-day ventilator-free days, and ICU LOS among patients with VDRF. These findings are consistent with existing literature that has hypothesized that obesity is not associated with worsened outcomes among patients with VDRF, including those with ARDS (5, 28), and builds on prior work by concluding that BMI was not associated with worse clinical outcomes for all cases of VDRF. To our knowledge, our

cohort is the largest to date addressing the influence of obesity in VDRF and is representative of existing best practices at academic medical centers.

Despite almost one-third and one-fifth of patients in the severely obese and obese groups, respectively, having DP greater than or equal to 15 cm H_2O, there was no association between mortality and BMI class in our cohort. Secondary analysis of existing ARDS clinical trials has found DP and E_{rs} to be strongly associated with survival among patients with ARDS (27, 29). In contrast, similar associations between mortality and elevated DP in patients without ARDS have been inconsistent. Sahetya et al (30) reported a 36% increase in the odds of mortality for every 7 cm H_2O increase in DP among patients without ARDS; however, Lanspa et al (31) did not find any significant associations with 30-day mortality and DP among patients without ARDS. Similarly, Schmidt et al (32) only found associations between DP and mortality among patients with ARDS or Pao_2/Fio_2 less than 300 mm Hg. While these studies highlight a potential key difference in the physiology and response to ventilation between patients with ARDS and without ARDS, these prior cohorts did not consider how BMI may influence DP, which our results show is strongly correlated with BMI class.

Prior studies have concluded that E_{rs} is increased in spontaneous and mechanically ventilated patients with obesity with normal lungs (15, 33). Increases in chest wall elastance contribute to this phenomenon and may help to mitigate the potential for injury from elevated DP by limiting end-inspiratory transmural pressures. However, physiology studies in anesthetized and paralyzed obese patients undergoing surgery have also demonstrated that increases in lung elastance may be responsible for an equal or greater proportion of the observed increases in E_{RS} (15, 33). Indeed, in a recent crossover study, when severely obese VDRF patients underwent an esophageal manometry-guided PEEP titration, mean E_{RS} decreased by 23%, largely due to improvement in lung elastance during alveolar recruitment (34). Likewise, a small crossover study among obese patients with ARDS found that DP was significantly reduced with a recruitment maneuver and decremental PEEP strategy (35). A subsequent cohort study showed that esophageal manometry-guided ventilator settings significantly reduced DP while significantly increasing PEEP in morbidly obese patients with ARDS (36). These findings suggest obese and severely obese patients with VDRF have DP and E_{rs} that are more susceptible to poor lung recruitment than normal or overweight individuals. If not adequately recruited, measured DP and E_{RS} will likely be higher among obese and severely obese VDRF patients, potentially leading clinicians to mistakenly assume that these measurements are reflective of intrinsic lung stiffness and erroneously reducing their Vt or their PEEP.

As supported by the aforementioned studies, we hypothesize elevated DP among obese and severely obese VDRF patients mostly reflect systematically poor lung recruitment with existing methods for titrating PEEP. We were unable to identify whether patients had undergone recruitment maneuvers prior to their initial PEEP settings, as this was not recorded in the EHR data used for our cohort. Nevertheless, our findings have important implications for existing LPV practice and future DP-limited ventilation strategies. Based on our findings, elevated DP among obese and severely obese VDRF patients, while common in clinical practice, is not associated with worsened outcomes, likely due to elevated DP being more reflective of poor lung recruitment with existing PEEP titration strategies than intrinsic lung pathology. Future efforts to prospectively test DP-guided ventilation strategies should include and stratify VDRF patients by their BMI and consider routine recruitment maneuvers in obese and severely patients to ensure DP thresholds for LPV are prognostically informative.

Limitations of our study include possible unaccounted bias due to its observational study design and missingness in our dataset. While data missingness could introduce bias into our analysis, we have addressed this using a validated strategy of multiple imputation to minimize bias (26). Second, we conducted a sensitivity analysis using CCA for our three main outcome models for the RR of in-hospital mortality, high DP, and high E_{RS}. These analyses found no statistically significant difference in RR from the main analyses, which used multiple imputation. However, as expected, due to smaller sample sizes resulting from missing covariate data, the CIs of the complete case analyses were somewhat larger than the main analyses. As a result of these sensitivity analyses, we can see our findings are robust to our choice for handling missing data.

In summary, obese and severely obese VDRF patients have significantly higher DP and E_{rs} despite adherence to LPV but have no differences in in-hospital

mortality, ventilator-free days, and ICU LOS. Further research should include prospective clinical trials to determine how existing LPV strategies should be adapted to better reflect the unique respiratory physiology for this patient population.

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